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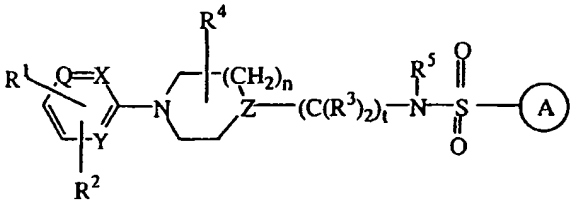
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(54) Title: SULFONYLAMINO-DERIVATIVES AS NOVEL INHIBITORS OF HISTONE DEACETYLASE



(I)

(57) Abstract: This invention comprises the novel compounds of formula (I)wherein n, m, t, R^1, R^2, R^3, R^4, R^5, L, Q, X, Y, Z and have defined meanings, having histone deacetylase inhibiting enzymatic activity; their preparation, compositions containing them and their use as a medicine.

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SULFONYLAMINO-DERIVATIVES AS NOVEL INHIBITORS OF HISTONE DEACETYLASE.

This invention concerns compounds having histone deacetylase (HDAC) inhibiting enzymatic activity. It further relates to processes for their preparation, to compositions comprising them, as well as their use, both *in vitro* and *in vivo*, to inhibit HDAC and as a medicine, for instance as a medicine to inhibit proliferative conditions, such as cancer and psoriasis.

In all eukaryotic cells, genomic DNA in chromatine associates with histones to form nucleosomes. Each nucleosome consists of a protein octamer made up of two copies of each histones H2A, H2B, H3 and H4. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. The most common posttranslational modification of these core histones is the reversible acetylation of the ε-amino groups of conserved, highly basic N-terminal lysine residues. The steady state of histone acetylation is established by the dynamic equilibrium between competing histone acetyltransferase(s) and histone deacetylase(s) herein referred to as "HDAC". Histone acetylation and deacetylation has long been linked to transcriptional control. The recent cloning of the genes encoding different histone acetyltransferases and histone deacetylases provided a possible explanation for the relationship between histone acetylation and transcriptional control. The reversible acetylation of histones can result in chromatin remodelling and as such act as a control mechanism for gene transcription. In general, hyperacetylation of histones facilitates gene expression, whereas histone deacetylation is correlated with transcriptional repression. Histone acetyltransferases were shown to act as transcriptional coactivators, whereas histone deacetylases were found to belong to transcriptional repression pathways.
The dynamic equilibrium between histone acetylation and deacetylation is essential for normal cell growth. Inhibition of histone deacetylase results in cell cycle arrest, cellular differentiation, apoptosis and reversal of the transformed phenotype. Therefore HDAC inhibitors can have great therapeutic potential in the treatment of cell proliferative diseases or conditions (Marks et al., Nature Reviews: Cancer 1: 194-202, 2001)

The study of inhibitors of histone deacetylases (HDAC) indicates that indeed these enzymes play an important role in cell proliferation and differentiation. The inhibitor Trichostatin A (TSA) causes cell cycle arrest at both G1 and G2 phases, reverts the transformed phenotype of different cell lines, and induces differentiation of Friend

leukemia cells and others. TSA (and suberoylanilide hydroxamic acid SAHA) have been reported to inhibit cell growth, induce terminal differentiation, and prevent the formation of tumours in mice (Finnin et al., Nature, 401: 188-193, 1999).

Trichostatin A has also been reported to be useful in the treatment of fibrosis, e.g. liver fibrosis and liver chirrhosis. (Geerts et al., European Patent Application EP 0 827 742, published 11 March, 1998).

Patent application WO01/38322 published on May 31, 2001 discloses amongst others inhibitors of histone deacetylase of general formula Cy-L^1-Ar-Y^1-C(O)-NH-Z, providing compositions and methods for treating cell proliferative diseases and conditions.

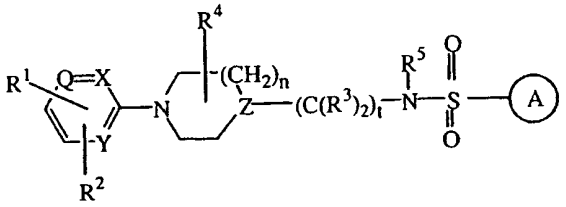
Patent application WO01/70675 published on 27 September, 2001 discloses inhibitors of histone deacetylase of formula Cy-$S(O)_2$-NH-Y^3-W and further provides compositions and methods for treating cell proliferative diseases and conditions.

The problem to be solved is to provide histone deacetylase inhibitors with high enzymatic activity and also show advantageous properties such as cellular activity and increased bioavailability, preferably oral bioavailability, and have little or no side effects.

The novel compounds of the present invention solve the above-described problem. The compounds differ from the prior art in structure.

The compounds of the present invention show excellent *in-vitro* histone deacetylase inhibiting enzymatic activity. The present compounds have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). The compounds of the present invention show good metabolic stability and high bioavailability and more particular they show oral bioavailability. Moreover, the compounds of the present invention have a low affinity for the P450 enzymes, which reduces the risk of adverse drug-drug interaction allowing also for a wider safety margin.

This invention concerns compounds of formula (I)



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

t is 0, 1, 2, 3 or 4 and when t is 0 then a direct bond is intended;

each Q is nitrogen or ;

each X is nitrogen or ;

each Y is nitrogen or ;

each Z is nitrogen or ;

R^1 is $-C(O)NR^8R^9$, $-N(H)C(O)R^{10}$, $-C(O)-C_{1-6}$alkanediylSR^{10}, $-NR^{11}C(O)N(OH)R^{10}$, $-NR^{11}C(O)C_{1-6}$alkanediylSR^{10}, $-NR^{11}C(O)C{=}N(OH)R^{10}$ or another Zn-chelating-group
wherein R^8 and R^9 are each independently selected from hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl or aminoaryl;
R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, arylC_{1-6}alkyl, C_{1-6}alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
R^{11} is independently selected from hydrogen or C_{1-6}alkyl;

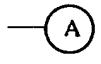
R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, di(C_{1-6}alkyl)amino, hydroxyamino or naphtalenylsulfonylpyrazinyl;

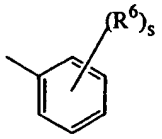
each R^3 independently represents a hydrogen atom and one hydrogen atom can be replaced by a substituent selected from aryl;

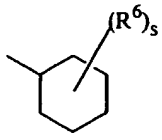
R^4 is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, hydroxycarbonyl, aminoC_{1-6}alkyl,

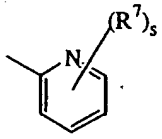
aminocarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyaminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

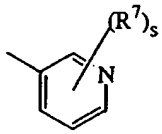
R^5 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl or aryl;

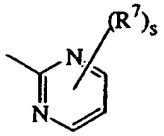

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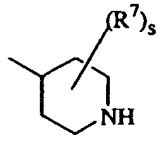

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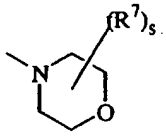

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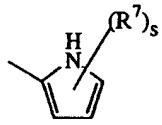

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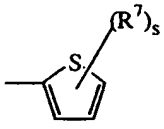

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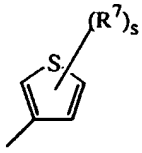

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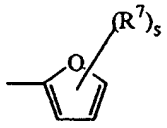

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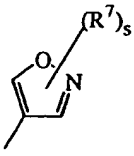

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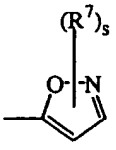

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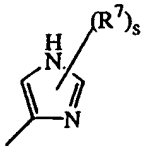

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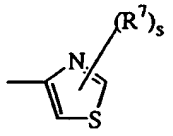

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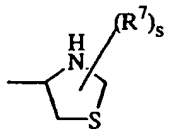

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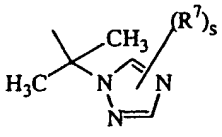

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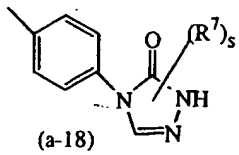

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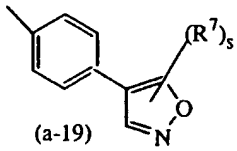

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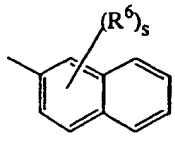

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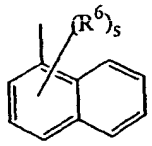

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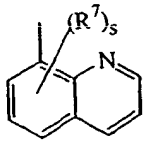

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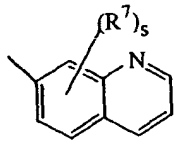

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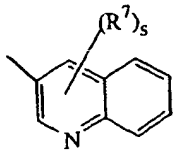

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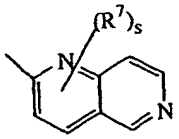

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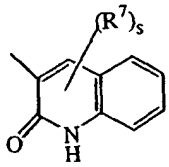

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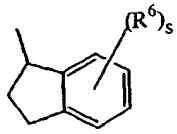

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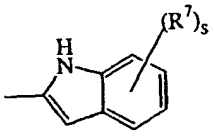

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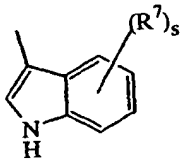

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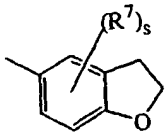

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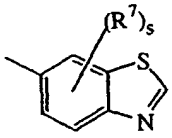

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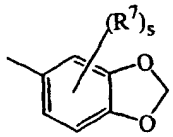

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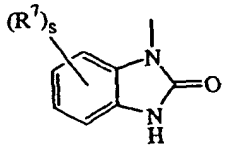

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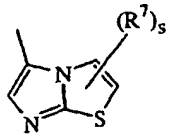

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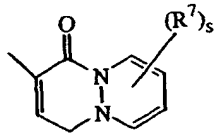

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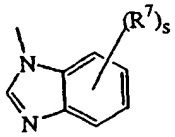

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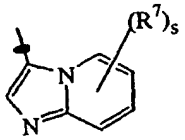

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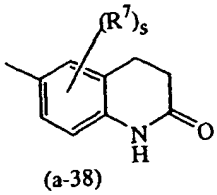

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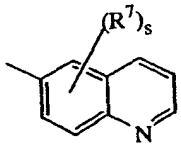

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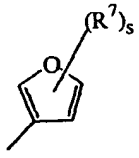

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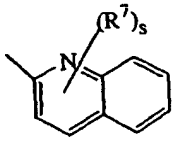

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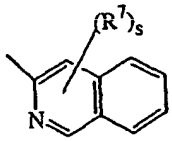

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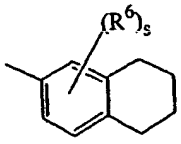

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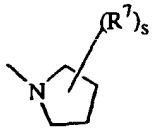

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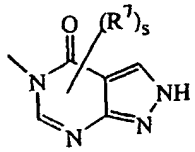

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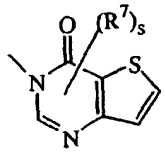

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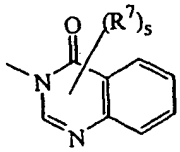

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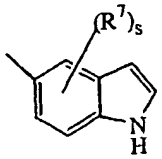

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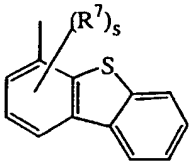

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(a-45)

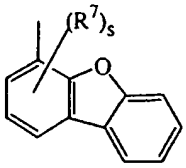

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(a-47)

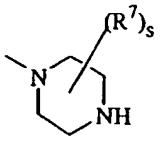

(a-48)



(a-49)



(a-50)



(a-51)

wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R^6 and R^7 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyl substituted with aryl and C_{3-10}cycloalkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; cyanoC_{1-6}alkyl; hydroxyC_{1-6}alkyl; hydroxyC_{1-6}alkyloxy; hydroxyC_{1-6}alkylamino; aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminocarbonyl; di(hydroxyC_{1-6}alkyl)amino; (aryl)(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminoC_{1-6}alkylamino; di(C_{1-6}alkyl)aminoC_{1-6}alkylaminoC_{1-6}alkyl; arylsulfonyl; arylsulfonylamino; aryloxy; aryloxyC_{1-6}alkyl; arylC_{2-6}alkenediyl; di(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)amino(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)amino(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; aminosulfonylamino(C_{1-6}alkyl)amino; aminosulfonylamino(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylamino(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminosulfonylamino(C_{1-6}alkyl)aminoC_{1-6}alkyl; cyano; thiophenyl; thiophenyl substituted with di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylpiperazinylC_{1-6}alkyl, hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl, hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl, di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl, C_{1-6}alkyloxypiperidinyl, C_{1-6}alkyloxypiperidinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxyC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, or di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; furanyl; furanyl substituted with hydroxyC_{1-6}alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}alkyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; piperidinylC_{1-6}alkyloxy; morpholinyl; C_{1-6}alkylmorpholinyl; morpholinylC_{1-6}alkyloxy; morpholinylC_{1-6}alkyl; morpholinylC_{1-6}alkylamino; morpholinylC_{1-6}alkylaminoC_{1-6}alkyl; piperazinyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinylC_{1-6}alkyloxy; piperazinylC_{1-6}alkyl; naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl;

C_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkylpiperazinylC_{1-6}alkylamino; C_{1-6}alkylpiperazinylC_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC_{1-6}alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylpiperazinyl; di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl; hydroxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkyloxypiperidinyl; C_{1-6}alkyloxypiperidinylC_{1-6}alkyl; piperidinylaminoC_{1-6}alkylamino; piperidinylaminoC_{1-6}alkylaminoC_{1-6}alkyl; (C_{1-6}alkylpiperidinyl)(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkylamino; (C_{1-6}alkylpiperidinyl)(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkylaminoC_{1-6}alkyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)amino; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl; hydroxyC_{1-6}alkylaminoC_{1-6}alkyl; di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy, aryloxy or aryl; pyrimidinyl; tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC_{1-6}alkyl; quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC_{1-4}alkyloxy, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxyC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminocarbonyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)amino(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)amino(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)aminoC_{1-4}alkyl, aminosulfonylamino(C_{1-4}alkyl)amino, aminosulfonylamino(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminosulfonylamino(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminosulfonylamino(C_{1-4}alkyl)aminoC_{1-6}alkyl, cyano, piperidinylC_{1-4}alkyloxy, pyrrolidinylC_{1-4}alkyloxy, aminosulfonylpiperazinyl, aminosulfonylpiperazinylC_{1-4}alkyl, di(C_{1-4}alkyl)aminosulfonylpiperazinyl, di(C_{1-4}alkyl)aminosulfonylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylpiperazinyl, hydroxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkyloxypiperidinyl, C_{1-4}alkyloxypiperidinylC_{1-4}alkyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinylC_{1-4}alkyl,

(hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)amino, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(hydroxyC_{1-4}alkyl)amino, di(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkyl, furanyl substituted with –CH=CH-CH=CH-, pyrrolidinylC_{1-4}alkyl, pyrrolidinylC_{1-4}alkyloxy, morpholinyl, morpholinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyl, morpholinylC_{1-4}alkylamino, morpholinylC_{1-4}alkylaminoC_{1-4}alkyl, piperazinyl, C_{1-4}alkylpiperazinyl, C_{1-4}alkylpiperazinylC_{1-4}alkyloxy, piperazinylC_{1-4}alkyl, C_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkylpiperazinylC_{1-4}alkylamino, C_{1-4}alkylpiperazinylC_{1-4}alkylaminoC_{1-6}alkyl, tetrahydropyrimidinylpiperazinyl, tetrahydropyrimidinylpiperazinylC_{1-4}alkyl, piperidinylaminoC_{1-4}alkylamino, piperidinylaminoC_{1-4}alkylaminoC_{1-4}alkyl, (C_{1-4}alkylpiperidinyl)(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkylamino, (C_{1-4}alkylpiperidinyl)(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkylaminoC_{1-4}alkyl, pyridinylC_{1-4}alkyloxy, hydroxyC_{1-4}alkylamino, hydroxyC_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkylamino, aminothiadiazolyl, aminosulfonylpiperazinylC_{1-4}alkyloxy, or thiophenylC_{1-4}alkylamino;

each R^6 and R^7 can be placed on the nitrogen in replacement of the hydrogen;

aryl in the above is phenyl, or phenyl substituted with one or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

The term "histone deacetylase inhibitor" or "inhibitor of histone deacetylase" is used to identify a compound, which is capable of interacting with a histone deacetylase and inhibiting its activity, more particularly its enzymatic activity. Inhibiting histone deacetylase enzymatic activity means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. Preferably, such inhibition is specific, i.e. the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce some other, unrelated biological effect.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, e.g. methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl includes C_{1-4}alkyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, pentyl, 2-methyl-butyl, hexyl, 2-methylpentyl and the like; C_{1-6}alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl 1,4-butanediyl,

1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof such as, 2-methylpentanediyl, 3-methylpentanediyl, 2,2-dimethylbutanediyl, 2,3-dimethylbutanediyl and the like; trihaloC_{1-6}alkyl defines C_{1-6}alkyl containing three identical or different halo substituents for example trifluoromethyl; C_{2-6}alkenediyl defines bivalent straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenediyl, 2-propenediyl, 3-butenediyl, 2-pentenediyl, 3-pentenediyl, 3-methyl-2-butenediyl, and the like; aminoaryl defines aryl substituted with amino; and C_{3-10}cycloalkyl includes cyclic hydrocarbon groups having from 3 to 10 carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl and the like.

The term "another Zn-chelating group" refers to a group, which is capable of interacting with a Zn-ion, which can be present at an enzymatic binding site.

Pharmaceutically acceptable addition salts encompass pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts. The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms, which the compounds of formula (I) are able to form. The compounds of formula (I) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, trifluoroacetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.
The compounds of formula (I) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.
The term "acid or base addition salts" also comprises the hydrates and the solvent addition forms, which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "stereochemically isomeric forms of compounds of formula (I)", as used herein, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures, which are not interchangeable, which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms, which said compound might possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more of the piperidine-, piperazine or pyridazinyl-nitrogens are *N*-oxidized.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to include also the pharmaceutically acceptable addition salts and all stereoisomeric forms.

As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ε-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Human HDAC proteins or gene products, include, but are not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9 and HDAC-10. The histone deacetylase can also be derived from a protozoal or fungal source.

A first group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) n is 0, 1 or 2;

b) t is 0, 1, 2 or 3;

c) each Q is ;

d) R^1 is –C(O)NH(OH) or $-NR^{11}C(O)C{=}N(OH)R^{10}$ wherein R^{10} is arylC_{1-6}alkyl and R^{11} is hydrogen;

e) R^2 is hydrogen, C_{1-6}alkyl or naphtalenylsulfonylpyrazinyl;

f) each R^3 independently represents a hydrogen atom;

g) R^4 is hydrogen, hydroxy, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxy;

h) R^5 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;

i)  is a radical selected from (a-1), (a-7) or (a-20);

j) each s is independently 0 or 1;

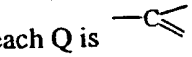
k) each R^6 is independently selected from hydrogen; thiophenyl; furanyl; benzofuranyl; phenyl; or phenyl substituted with one substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, C_{1-4}alkylsulfonyl or di(C_{1-4}alkyl)amino;

l) each R^7 is independently selected from hydrogen.

A second group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) n is 1 or 2;

b) t is 0, 1, 2 or 3;

c) each Q is ;

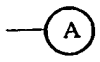
d) R^1 is –C(O)NH(OH);

e) R^2 is hydrogen or C_{1-6}alkyl;

f) each R^3 independently represents a hydrogen atom;

g) R^4 is hydrogen;

h) R^5 is hydrogen or C_{1-6}alkyloxyC_{1-6}alkyl;

i)  is a radical selected from (a-1) or (a-20);

j) each s is independently 0 or 1;

k) each R^6 is independently selected from hydrogen; thiophenyl; furanyl; benzofuranyl; phenyl; or phenyl substituted with one substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl or di(C_{1-4}alkyl)amino.

A third group of interesting compounds consists of those compounds of formula (I) wherein R^2 is hydrogen.

A fourth group of interesting compounds consists of those compounds of formula (I) wherein. R^1 is –C(O)NH(OH).

A fifth group of interesting compounds consists of those compounds of formula (I) wherein R^1 is –C(O)NH(OH) and R^2 is hydrogen.

A sixth group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) t is 0;

b) R^1 is $-C(O)NR^8R^9$, $-C(O)-C_{1-6}alkanediylSR^{10}$, $-NR^{11}C(O)N(OH)R^{10}$, $-NR^{11}C(O)C_{1-6}alkanediylSR^{10}$, $-NR^{11}C(O)C=N(OH)R^{10}$ or another Zn-chelating-group

wherein R^8 and R^9 are each independently selected from hydrogen, hydroxy, $hydroxyC_{1-6}alkyl$ or $aminoC_{1-6}alkyl$;

c) R^2 is hydrogen, halo, hydroxy, amino, nitro, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, trifluoromethyl or $di(C_{1-6}alkyl)amino$;

d) R^4 is hydrogen, hydroxy, amino, $hydroxyC_{1-6}alkyl$, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, $arylC_{1-6}alkyl$, aminocarbonyl, $aminoC_{1-6}alkyl$, $C_{1-6}alkylaminoC_{1-6}alkyl$ or $di(C_{1-6}alkyl)aminoC_{1-6}alkyl$;

e) R^5 is hydrogen

f)  is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) or (a-51);

g) each s is independently 0, 1, 2, 3 or 4;

h) R^6 is hydrogen; halo; hydroxy; amino; nitro; $trihaloC_{1-6}alkyl$; $trihaloC_{1-6}alkyloxy$; $C_{1-6}alkyl$; $C_{1-6}alkyloxy$; $C_{1-6}alkylcarbonyl$; $C_{1-6}alkyloxycarbonyl$; $C_{1-6}alkylsulfonyl$; $hydroxyC_{1-6}alkyl$; aryloxy; $di(C_{1-6}alkyl)amino$; cyano; thiophenyl; furanyl; furanyl substituted with $hydroxyC_{1-6}alkyl$; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and $C_{1-6}alkyl$; $C_{1-6}alkyltriazolyl$; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; $C_{1-6}alkylmorpholinyl$; piperazinyl; $C_{1-6}alkylpiperazinyl$; $hydroxyC_{1-6}alkylpiperazinyl$; $C_{1-6}alkyloxypiperidinyl$; pyrazoly; pyrazolyl substituted with one or two substituents selected from $C_{1-6}alkyl$ or $trihaloC_{1-6}alkyl$; pyridinyl; pyridinyl substituted with $C_{1-6}alkyloxy$, aryloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$ or trifluoromethyl;

i) R^7 is hydrogen; halo; hydroxy; amino; nitro; $trihaloC_{1-6}alkyl$; $trihaloC_{1-6}alkyloxy$; $C_{1-6}alkyl$; $C_{1-6}alkyloxy$; $C_{1-6}alkylcarbonyl$; $C_{1-6}alkyloxycarbonyl$;

C_{1-6}alkylsulfonyl; hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; pyridinyl; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

A seventh group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) R^8 and R^9 are each independently selected from hydrogen, hydroxy, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl or aminoaryl;

b) R^5 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

c)  is a radical selected from (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-27), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42) (a-43) or (a-44);

d) each R^6 and R^7 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkylsulfonyl; cyanoC_{1-6}alkyl; hydroxyC_{1-6}alkyl; hydroxyC_{1-6}alkyloxy; hydroxyC_{1-6}alkylamino; aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminocarbonyl; di(hydroxyC_{1-6}alkyl)amino; arylC_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminoC_{1-6}alkylamino; arylsulfonyl; arylsulfonylamino; aryloxy; arylC_{2-6}alkenediyl; di(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; cyano; thiophenyl; thiophenyl substituted with di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylpiperazinylC_{1-6}alkyl or di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; furanyl; imidazolyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; piperidinylC_{1-6}alkyloxy; morpholinyl; C_{1-6}alkylmorpholinyl; morpholinylC_{1-6}alkyloxy; morpholinylC_{1-6}alkyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinylC_{1-6}alkyloxy; C_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC_{1-6}alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylpiperazinyl; di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl; hydroxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkyloxypiperidinyl; C_{1-6}alkyloxypiperidinylC_{1-6}alkyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl;

(hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)amino; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy, aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)aminoC_{1-4}alkyl, piperidinylC_{1-4}alkyloxy, pyrrolidinylC_{1-4}alkyloxy, aminosulfonylpiperazinyl, aminosulfonylpiperazinylC_{1-4}alkyl, di(C_{1-4}alkyl)aminosulfonylpiperazinyl, di(C_{1-4}alkyl)aminosulfonylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylpiperazinyl, hydroxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkyloxypiperidinyl, C_{1-4}alkyloxypiperidinylC_{1-4}alkyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)amino, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)aminoC_{1-4}alkyl, pyrrolidinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyl, C_{1-4}alkylpiperazinyl, C_{1-4}alkylpiperazinylC_{1-4}alkyloxy, C_{1-4}alkylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylamino, di(hydroxyC_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkylamino, aminothiadiazolyl, aminosulfonylpiperazinylC_{1-4}alkyloxy, or thiophenylC_{1-4}alkylamino.

A group of preferred compounds consists of those compounds of formula (I) wherein

R^8 and R^9 are each independently selected from hydrogen, hydroxy, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl or aminoaryl;

R^5 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

—(A) is a radical selected from (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-27), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42) (a-43) or (a-44);

each R^6 and R^7 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkylsulfonyl; cyanoC_{1-6}alkyl; hydroxyC_{1-6}alkyl; hydroxyC_{1-6}alkyloxy; hydroxyC_{1-6}alkylamino;

aminoC$_{1-6}$alkyloxy; di(C$_{1-6}$alkyl)aminocarbonyl; di(hydroxyC$_{1-6}$alkyl)amino; arylC$_{1-6}$alkyl)amino; di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyloxy; di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkylamino; arylsulfonyl; arylsulfonylamino; aryloxy; arylC$_{2-6}$alkenediyl; di(C$_{1-6}$alkyl)amino; di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl; di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl; cyano; thiophenyl; thiophenyl substituted with di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, C$_{1-6}$alkylpiperazinylC$_{1-6}$alkyl or di(hydroxyC$_{1-6}$alkyl)aminoC$_{1-6}$alkyl; furanyl; imidazolyl; C$_{1-6}$alkyltriazolyl; tetrazolyl; pyrrolidinyl; piperidinylC$_{1-6}$alkyloxy; morpholinyl; C$_{1-6}$alkylmorpholinyl; morpholinylC$_{1-6}$alkyloxy; morpholinylC$_{1-6}$alkyl; C$_{1-6}$alkylpiperazinyl; C$_{1-6}$alkylpiperazinylC$_{1-6}$alkyloxy; C$_{1-6}$alkylpiperazinylC$_{1-6}$alkyl; C$_{1-6}$alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC$_{1-6}$alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC$_{1-6}$alkyl; di(C$_{1-6}$alkyl)aminosulfonylpiperazinyl; di(C$_{1-6}$alkyl)aminosulfonylpiperazinylC$_{1-6}$alkyl; hydroxyC$_{1-6}$alkylpiperazinyl; hydroxyC$_{1-6}$alkylpiperazinylC$_{1-6}$alkyl; C$_{1-6}$alkyloxypiperidinyl; C$_{1-6}$alkyloxypiperidinylC$_{1-6}$alkyl; hydroxyC$_{1-6}$alkyloxyC$_{1-6}$alkylpiperazinyl; hydroxyC$_{1-6}$alkyloxyC$_{1-6}$alkylpiperazinylC$_{1-6}$alkyl; (hydroxyC$_{1-6}$alkyl)(C$_{1-6}$alkyl)amino; (hydroxyC$_{1-6}$alkyl)(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl; pyrrolidinylC$_{1-6}$alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C$_{1-6}$alkyl or trihaloC$_{1-6}$alkyl; pyridinyl; pyridinyl substituted with C$_{1-6}$alkyloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, C$_{1-6}$alkyl, C$_{1-6}$alkyloxy, hydroxyC$_{1-4}$alkyl; trifluoromethyl, trifluoromethyloxy, hydroxyC$_{1-4}$alkyloxy, C$_{1-4}$alkyloxyC$_{1-4}$alkyloxy, aminoC$_{1-4}$alkyloxy, di(C$_{1-4}$alkyl)aminoC$_{1-4}$alkyloxy, di(C$_{1-4}$alkyl)amino, di(C$_{1-4}$alkyl)aminoC$_{1-4}$alkyl, di(C$_{1-4}$alkyl)aminoC$_{1-4}$alkyl(C$_{1-4}$alkyl)aminoC$_{1-4}$alkyl, piperidinylC$_{1-4}$alkyloxy, pyrrolidinylC$_{1-4}$alkyloxy; aminosulfonylpiperazinyl, aminosulfonylpiperazinylC$_{1-4}$alkyl, di(C$_{1-4}$alkyl)aminosulfonylpiperazinyl, di(C$_{1-4}$alkyl)aminosulfonylpiperazinylC$_{1-4}$alkyl, hydroxyC$_{1-4}$alkylpiperazinyl, hydroxyC$_{1-4}$alkylpiperazinylC$_{1-4}$alkyl, C$_{1-4}$alkyloxypiperidinyl, C$_{1-4}$alkyloxypiperidinylC$_{1-4}$alkyl, hydroxyC$_{1-4}$alkyloxyC$_{1-4}$alkylpiperazinyl, hydroxyC$_{1-4}$alkyloxyC$_{1-4}$alkylpiperazinylC$_{1-4}$alkyl, (hydroxyC$_{1-4}$alkyl)(C$_{1-4}$alkyl)amino, (hydroxyC$_{1-4}$alkyl)(C$_{1-4}$alkyl)aminoC$_{1-4}$alkyl, pyrrolidinylC$_{1-4}$alkyloxy, morpholinylC$_{1-4}$alkyloxy, morpholinylC$_{1-4}$alkyl, C$_{1-4}$alkylpiperazinyl, C$_{1-4}$alkylpiperazinylC$_{1-4}$alkyloxy, C$_{1-4}$alkylpiperazinylC$_{1-4}$alkyl, hydroxyC$_{1-4}$alkylamino, di(hydroxyC$_{1-4}$alkyl)amino,

di(C_{1-4}alkyl)aminoC_{1-4}alkylamino, aminothiadiazolyl, aminosulfonylpiperazinylC_{1-4}alkyloxy, or thiophenylC_{1-4}alkylamino.

A further group of preferred compounds consists of those compounds of formula (I) wherein t is 0;

R^1 is $-C(O)NR^8R^9$, $-C(O)-C_{1-6}$alkanediylSR^{10}, $-NR^{11}C(O)N(OH)R^{10}$, $-NR^{11}C(O)C_{1-6}$alkanediylSR^{10}, $-NR^{11}C(O)C=N(OH)R^{10}$ or another Zn-chelating-group wherein R^8 and R^9 are each independently selected from hydrogen, hydroxy, hydroxyC_{1-6}alkyl or aminoC_{1-6}alkyl;

R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl or di(C_{1-6}alkyl)amino;

R^4 is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^5 is hydrogen;

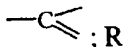
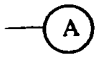

is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) or (a-51);

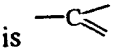
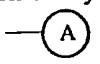
each s is independently 0, 1, 2, 3 or 4;

R^6 is hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; thiophenyl; furanyl; furanyl substituted with hydroxyC_{1-6}alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}alkyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; C_{1-6}alkylmorpholinyl; piperazinyl; C_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinyl; C_{1-6}alkyloxypiperidinyl; pyrazoly; pyrazolyl substituted with one or two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy, aryloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

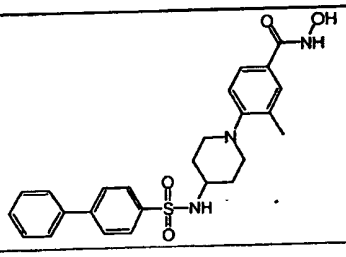
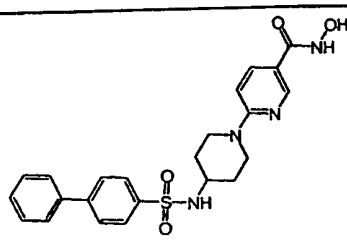
R^7 is hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; pyridinyl; phenyl; or phenyl

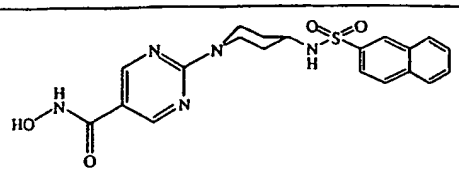
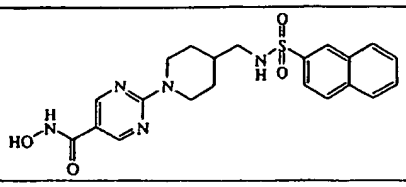
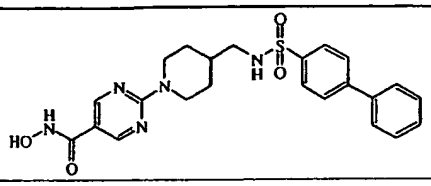
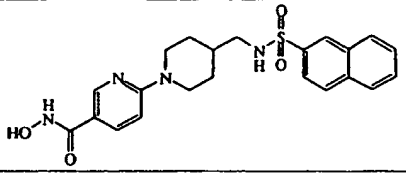
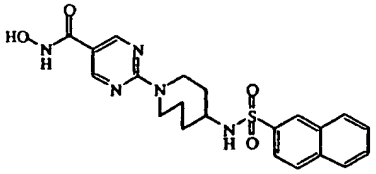
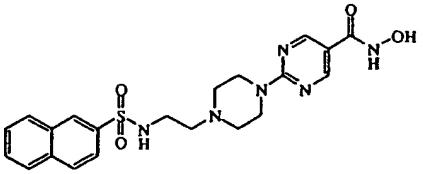
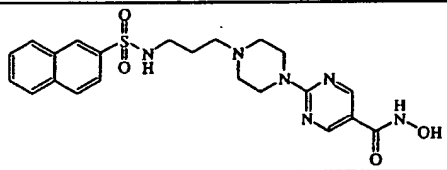
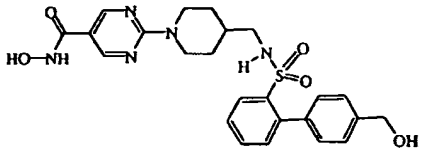
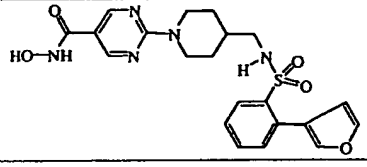
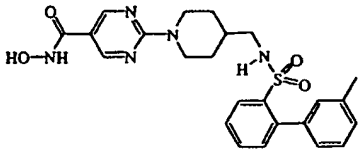
substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

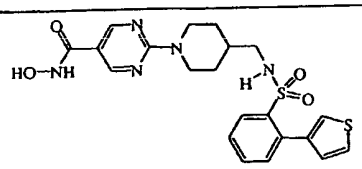
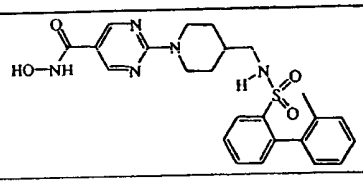
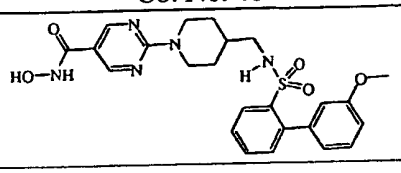
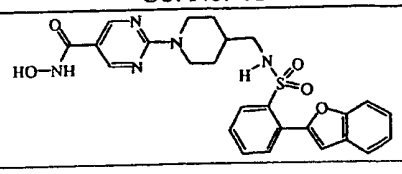
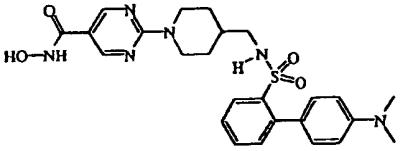
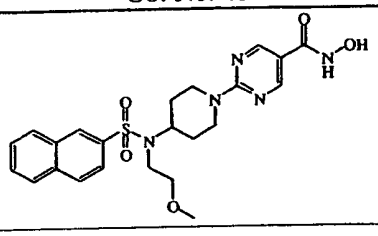
A group of more preferred compounds consists of those compounds of formula (I) wherein n is 0, 1 or 2; t is 0, 1, 2 or 3; each Q is  ; R^1 is –C(O)NH(OH) or $-NR^{11}C(O)C=N(OH)R^{10}$ wherein R^{10} is arylC_{1-6}alkyl and R^{11} is hydrogen; R^2 is hydrogen, C_{1-6}alkyl or naphtalenylsulfonylpyrazinyl; each R^3 independently represents a hydrogen atom; R^4 is hydrogen, hydroxy, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxy; R^5 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;  is a radical selected from (a-1), (a-7) or (a-20); each s is independently 0 or 1; each R^6 is independently selected from hydrogen; thiophenyl; furanyl; benzofuranyl; phenyl; or phenyl substituted with one substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, C_{1-4}alkylsulfonyl or di(C_{1-4}alkyl)amino and each R^7 is independently selected from hydrogen.

A group of even more preferred compounds consists of those compounds of formula (I) wherein n is 1 or 2; t is 0, 1, 2 or 3; each Q is  ; R^1 is –C(O)NH(OH); R^2 is hydrogen or C_{1-6}alkyl; each R^3 independently represents a hydrogen atom; R^4 is hydrogen; R^5 is hydrogen or C_{1-6}alkyloxyC_{1-6}alkyl;  is a radical selected from (a-1) or (a-20); each s is independently 0 or 1; and each R^6 is independently selected from hydrogen; thiophenyl; furanyl; benzofuranyl; phenyl; or phenyl substituted with one substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl or di(C_{1-4}alkyl)amino.

Most preferred compounds are compounds No. 13, No. 15, No. 2, No. 5, No. 21, No. 4, No. 24, No. 32, No. 26, No. 36, No. 38, No. 39, No. 40, No. 41, No. 42, No. 43, No. 44 and No. 35.

	
Co. No. 13	Co. No. 15

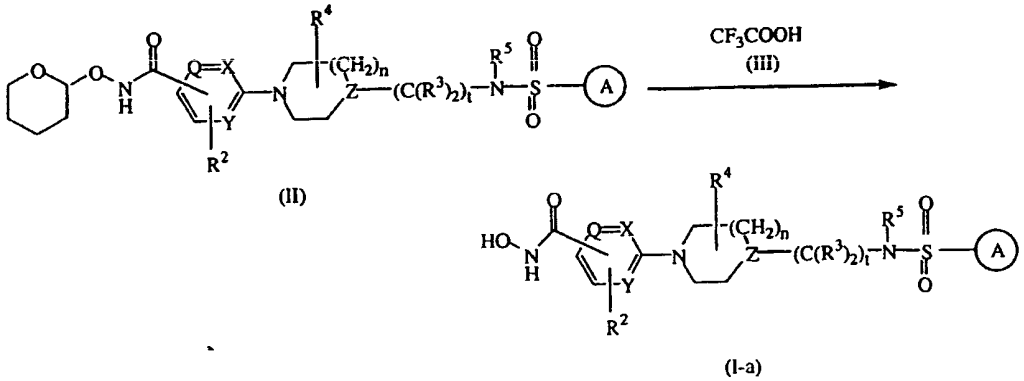
	
Co. No. 2	Co. No. 5
	
.0.7 CH_3OH; Co. No. 21	Co. No. 4
	
.0.23 $C_6H_{14}O$; Co. No. 24	.0.82 $C_2HF_3O_2$.0.82 H_2O; Co. No. 32
	
.0.85 $C_2HF_3O_2$.1.11 H_2O Co. No. 26	Co. No. 36
	
Co. No. 38	Co. No. 39

	
Co. No. 40	Co. No. 41
	
Co. No. 42	Co. No. 43
	
Co. No. 44	Co. No. 35

The compounds of formula (I) and their pharmaceutically acceptable salts and N-oxides and stereochemically isomeric forms thereof may be prepared in conventional manner.

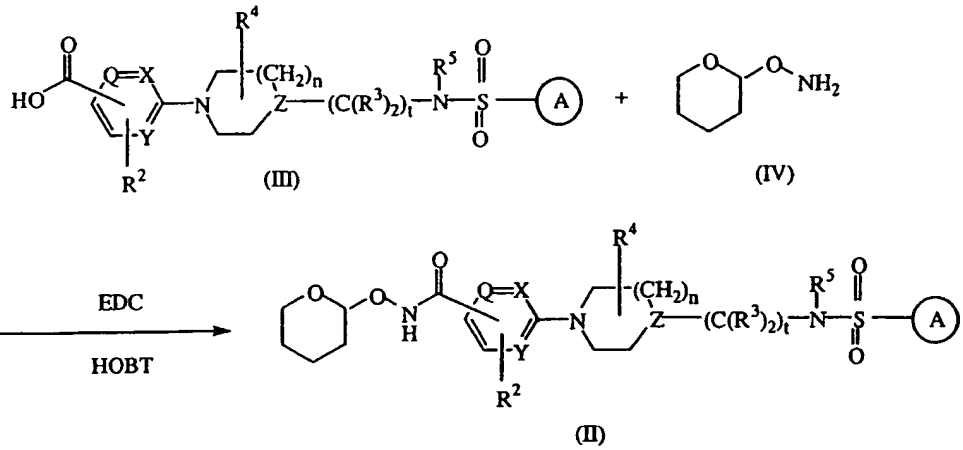
Two general synthesis routes are encompassed as example:

1a) Hydroxamic acids of formula (I) wherein R^1 is –C(O)NH(OH), said compounds being referred to as compounds of formula (I-a), may be prepared by reacting an intermediate of formula (II) with an appropriate acid, such as for example, trifluoro acetic acid. Said reaction is performed in an appropriate solvent, such as, for example, methanol.



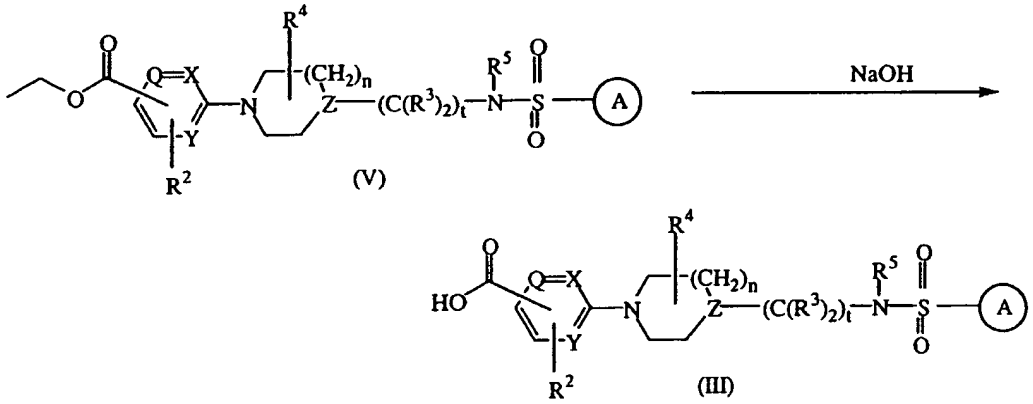
1b) intermediates of formula (II) may be prepared by reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of appropriate reagents such as *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine,

monohydrochloride (EDC) and 1-hydroxy-1*H*-benzotriazole (HOBT). The reaction may be performed in a suitable solvent such as a mixture of DCM and THF.



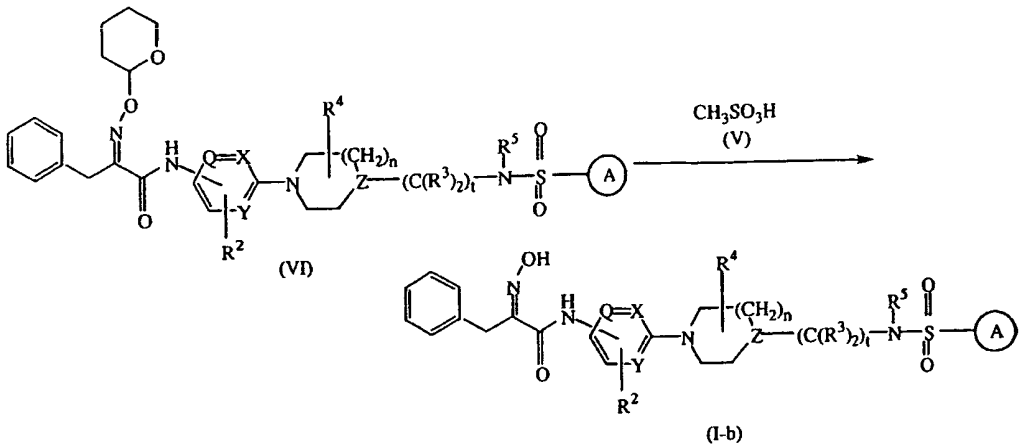
(III) (IV) (II)

1c) intermediates of formula (III) may be prepared by reacting an intermediate of formula (V) with an appropriate base such as NaOH in the presence of a suitable solvent such as ethanol.



(V) (III)

2) Compounds of formula (I) wherein R^1 is -NHC(O)C=N(OH)R^{10} wherein R^{10} is arylC_{1-6}alkyl' said compounds being referred to as compounds of formula (I-b), may be prepared by reacting an intermediate of formula (VI) with an appropriate acid, such as for example, methane sulfonic acid. Said reaction is performed in an appropriate solvent, such as, for example, methanol.



The compounds of formula (I) can also conveniently be prepared using solid phase synthesis techniques. In general, solid phase synthesis involves reacting an intermediate in a synthesis with a polymer support. This polymer-supported intermediate can then be carried on through a number of synthesis steps. After each step, filtering the resin and washing it numerous times with various solvents remove impurities. At each step the resin can be split up to react with various intermediates in the next step thus allowing for the synthesis of a large number of compounds. After the last step in the procedure the resin is treated with a reagent or process to cleave the resin from the sample. More detailed explanation of the techniques used in solid phase chemistry is described in for example "The Combinatorial Index" (B.Bunin, Academic Press) and Novabiochem's 1999 Catalogue & Peptide Synthesis Handbook (Novabiochem AG, Switzerland) both incorporated herein by reference.

The compounds of formula (I) and some of the intermediates may have at least one stereogenic centre in their structure. This stereogenic centre may be present in an R or an S configuration.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers, which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated there from by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific

stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereoisomeric forms thereof have valuable pharmacological properties in that they have a histone deacetylase (HDAC) inhibitory effect.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition). This includes the inhibition of tumour growth both directly by causing growth arrest, terminal differentiation and/or apoptosis of cancer cells, and indirectly, by inhibiting neovascularization of tumours.

This invention also provides a method for inhibiting tumour growth by administering an effective amount of a compound of the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumours by the administration of an effective amount of the compounds of the present invention. Examples of tumours which may be inhibited, but are not limited to, lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), prostate cancer including the advanced disease, hematopoietic tumours of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumours of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumour of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

The compound according to the invention may be used for other therapeutic purposes, for example:

a) the sensitisation of tumours to radiotherapy by administering the compound according to the invention before, during or after irradiation of the tumour for treating cancer;

b) treating arthropathies and osteopathological conditions such as rheumatoid arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis and systemic lupus erythematosus;

c) inhibiting smooth muscle cell proliferation including vascular proliferative disorders, atherosclerosis and restenosis;

d) treating inflammatory conditions and dermal conditions such as ulcerative colitis, Crohn's disease, allergic rhinitis, graft vs. host disease, conjunctivitis, asthma, ARDS, Behcets disease, transplant rejection, uticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, systemic lupus erythematosis, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis;

e) treating endometriosis, uterine fibroids, dysfunctional uterine bleeding and endometrial hyperplasia;

f) treating ocular vascularisation including vasculopathy affecting retinal and choroidal vessels;

g) treating a cardiac dysfunction;

h) inhibiting immunosuppressive conditions such as the treatment of HIV infections;

i) treating renal dysfunction;

j) suppressing endocrine disorders;

k) inhibiting dysfunction of gluconeogenesis;

l) treating a neuropathology for example Parkinson's disease or a neuropathology that results in a cognitive disorder, for example, Alzheimer's disease or polyglutamine related neuronal diseases;

m) inhibiting a neuromuscular pathology, for example, amylotrophic lateral sclerosis;

n) treating spinal muscular atrophy;

o) treating other pathologic conditions amenable to treatment by potentiating expression of a gene;

p) enhancing gene therapy.

Hence, the present invention discloses the compounds of formula (I) for use as a medicine as well as the use of these compounds of formula (I) for the manufacture of a medicament for treating one or more of the above-mentioned conditions.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereoisomeric forms thereof can have valuable diagnostic properties in that they can be

used for detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound and a HDAC.

The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances, etc. Examples of the radioisotopes include ^{125}I, ^{131}I, ^{3}H and ^{14}C. Enzymes are usually made detectable by conjugation of an appropriate substrate which, in turn catalyses a detectable reaction. Examples thereof include, for example, beta-galactosidase, beta-glucosidase, alkaline phosphatase, peroxidase and malate dehydrogenase, preferably horseradish peroxidase. The luminous substances include, for example, luminol, luminol derivatives, luciferin, aequorin and luciferase.

Biological samples can be defined as body tissue or body fluids. Examples of body fluids are cerebrospinal fluid, blood, plasma, serum, urine, sputum, saliva and the like.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case

appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Those skilled in the art could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that a therapeutically effective amount would be from 0.005 mg/kg to 100 mg/kg body weight, and in particular from 0.005 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.5 to 500 mg, and in particular 10 mg to 500 mg of active ingredient per unit dosage form.

As another aspect of the present invention a combination of a HDAC-inhibitor with another anticancer agent is envisaged, especially for use as a medicine, more specifically in the treatment of cancer or related diseases.

For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents. Examples of anti-cancer agents are:

- platinum coordination compounds for example cisplatin, carboplatin or oxalyplatin;
- taxane compounds for example paclitaxel or docetaxel;

- topoisomerase I inhibitors such as camptothecin compounds for example irinotecan or topotecan;
- topoisomerase II inhibitors such as anti-tumour podophyllotoxin derivatives for example etoposide or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- anti-tumour nucleoside derivatives for example 5-fluorouracil, gemcitabine or capecitabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine or lomustine;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin, idarubicin or mitoxantrone;
- HER2 antibodies for example trastuzumab;
- estrogen receptor antagonists or selective estrogen receptor modulators for example tamoxifen, toremifene, droloxifene, faslodex or raloxifene;
- aromatase inhibitors such as exemestane, anastrozole, letrazole and vorozole;
- differentiating agents such as retinoids, vitamin D and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine;
- kinase inhibitors for example flavoperidol, imatinib mesylate or gefitinib;
- farnesyltransferase inhibitors; or
- other HDAC inhibitors.

The term "platinum coordination compound" is used herein to denote any tumour cell growth inhibiting platinum coordination compound which provides platinum in the form of an ion.

The term "taxane compounds" indicates a class of compounds having the taxane ring system and related to or derived from extracts from certain species of yew (Taxus) trees.

The term "topisomerase inhibitors" is used to indicate enzymes that are capable of altering DNA topology in eukaryotic cells. They are critical for important cellular functions and cell proliferation. There are two classes of topoisomerases in eukaryotic cells, namely type I and type II. Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight. The enzyme binds to DNA and introduces a transient single-strand break, unwinds the double helix (or allows it to unwind) and subsequently reseals the break before dissociating from the DNA strand. Topisomerase

II has a similar mechanism of action which involves the induction of DNA strand breaks or the formation of free radicals.

The term "camptothecin compounds" is used to indicate compounds that are related to or derived from the parent camptothecin compound which is a water-insoluble alkaloid derived from the Chinese tree Camptothecin acuminata and the Indian tree Nothapodytes foetida.
The term "podophyllotoxin compounds" is used to indicate compounds that are related to or derived from the parent podophyllotoxin, which is extracted from the mandrake plant.

The term "anti-tumour vinca alkaloids" is used to indicate compounds that are related to or derived from extracts of the periwinkle plant (Vinca rosea).

The term "alkylating agents" encompass a diverse group of chemicals that have the common feature that they have the capacity to contribute, under physiological conditions, alkyl groups to biologically vital macromolecules such as DNA. With most of the more important agents such as the nitrogen mustards and the nitrosoureas, the active alkylating moieties are generated *in vivo* after complex degradative reactions, some of which are enzymatic. The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation in particular DNA synthesis and cell division. The capacity of alkylating agents to interfere with DNA function and integrity in rapidly proliferating tissues provides the basis for their therapeutic applications and for many of their toxic properties.

The term "anti-tumour anthracycline derivatives" comprise antibiotics obtained from the fungus *Strep. peuticus var. caesius* and their derivatives, characterised by having a tetracycline ring structure with an unusual sugar, daunosamine, attached by a glycosidic linkage.

Amplification of the human epidermal growth factor receptor 2 protein (HER 2) in primary breast carcinomas has been shown to correlate with a poor clinical prognosis for certain patients. Trastuzumab is a highly purified recombinant DNA-derived humanized monoclonal IgG1 kappa antibody that binds with high affiniity and specificity to the extracellular domain of the HER2 receptor.

Many breast cancers have estrogen receptors and growth of these tumours can be stimulated by estrogen. The terms "estrogen receptor antagonists" and "selective estrogen receptor modulators" are used to indicate competitive inhibitors of estradiol binding to the estrogen receptor (ER). Selective estrogen receptor modulators, when bond to the ER, induces a change in the three-dimensional shape of the receptor, inhibiting its binding to the estrogen responsive element (ERE) on DNA.

In postmenopausal women, the principal source of circulating estrogen is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition or inactivation is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer.

The term "antiestrogen agent" is used herein to include not only estrogen receptor antagonists and selective estrogen receptor modulators but also aromatase inhibitors as discussed above.

The term "differentiating agents" encompass compounds that can, in various ways, inhibit cell proliferation and induce differentiation. Vitamin D and retinoids are known to play a major role in regulating growth and differentiation of a wide variety of normal and malignant cell types. Retinoic acid metabolism blocking agents (RAMBA's) increase the levels of endogenous retinoic acids by inhibiting the cytochrome P450-mediated catabolism of retinoic acids.

DNA methylation changes are among the most common abnormalities in human neoplasia. Hypermethylation within the promotors of selected genes is usually associated with inactivation of the involved genes. The term "DNA methyl transferase inhibitors" is used to indicate compounds that act through pharmacological inhibition of DNA methyl transferase and reactivation of tumour suppressor gene expression.

The term "kinase inhibitors" comprises potent inhibitors of kinases that are involved in cell cycle progression and programmed cell death (apoptosis)

The term "farnesyltransferase inhibitors" is used to indicate compounds that were designed to prevent farnesylation of Ras and other intracellular proteins. They have been shown to have effect on malignant cell proliferation and survival.

The term "other HDAC inhibitors" comprises but is not limited to:

- short-chain fatty acids for example butyrate, 4-phenylbutyrate or valproic acid;
- hydroxamic acids for example suberoylanilide hydroxamic acid (SAHA), biaryl hydroxamate A-161906, bicyclic aryl-*N*-hydroxycarboxamides, pyroxamide, CG-1521, PXD-101, sulfonamide hydroxamic acid, LAQ-824, trichostatin A (TSA), oxamflatin, scriptaid, m-carboxy cinnamic acid bishydroxamic acid, or trapoxin-hydroxamic acid analogue;
- cyclic tetrapeptides for example trapoxin, apidicin or depsipeptide;
- benzamides for example MS-275 or CI-994, or
- depudecin.

For the treatment of cancer the compounds according to the present invention may be administered to a patient as described above, in conjunction with irradiation. Irradiation means ionising radiation and in particular gamma radiation, especially that emitted by linear accelerators or by radionuclides that are in common use today. The irradiation of the tumour by radionuclides can be external or internal.

The present invention also relates to a combination according to the invention of an anti-cancer agent and a HDAC inhibitor according to the invention.

The present invention also relates to a combination according to the invention for use in medical therapy for example for inhibiting the growth of tumour cells.

The present invention also relates to a combinations according to the invention for inhibiting the growth of tumour cells.

The present invention also relates to a method of inhibiting the growth of tumour cells in a human subject which comprises administering to the subject an effective amount of a combination according to the invention.

This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a combination according to the invention.

The other medicinal agent and HDAC inhibitor may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is

achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and HDAC inhibitor being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter (mg/m^2) of body surface area, for example 50 to 400 mg/m^2, particularly for cisplatin in a dosage of about 75 mg/m^2 and for carboplatin in about 300mg/m^2 per course of treatment.

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2, particularly for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2, particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment.

The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250mg/m^2, particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2, for vincristine in a dosage of about 1 to 2 mg/m^2, and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to1500 mg/m^2, particularly for 5-FU in a dosage of 200 to 500mg/m^2, for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 2500 mg/m^2 per course of treatment.

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2, particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2, particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2, for daunorubicin in a dosage of about 25 to 45mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

Trastuzumab is advantageously administered in a dosage of 1 to 5mg per square meter (mg/m^2) of body surface area, particularly 2 to 4mg/m^2 per course of treatment.

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14, 21 or 28 days.

In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the other medicinal agent and the HDAC inhibitor may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components.

The present invention therefore also relates to a pharmaceutical composition comprising the other medicinal agent and the HDAC inhibitor together with one or more pharmaceutical carriers.

The present invention also relates to a combination according to the invention in the form of a pharmaceutical composition comprising an anti-cancer agent and a HDAC inhibitor according to the invention together with one or more pharmaceutical carriers.

The present invention further relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting the growth of tumour cells.

The present invention further relates to a product containing as first active ingredient a HDAC inhibitor according to the invention and as second active ingredient an anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

Experimental part

The following examples are provided for purposes of illustration.

Hereinafter "BINAP" means 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, "BSA" means bovine serum albumine, "DCM" means dichloromethane, "DIC" means diisopropylcarbodiimide, "DIEA" means diisopropylethylamine, "DIPE" means diisopropyl ether", DMAP" means dimethylaminopyridine, "DMF" means dimethylformamide, "EDC" means N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine, monohydrochloride "DMSO" means dimethylsulfoxide, "EtOAc" means ethyl acetate, "Hepes" means 4-(-2-hydroxyethyl)-1-piperazine-ethanesulfonic acid, "iPrOH" means isopropyl, "HOBT" means 1-hydroxy-1*H*-benzotriazole, "MeOH" means methanol, "EtOH" means ethanol, "NMP" means N-methylpyrrolidinone, "TEA"means triethylamine, "TFA" means trifluoroacetic acid, "TIS" means triisopropylsilane, "THF" means tetrahydrofuran and "THP" means tetrahydropyranyl.

A. Preparation of the intermediates

Example A1

a) TEA (0.088 mol, 12.4ml) was added at 10°C to a solution of 4-amino-1-piperidinecarboxylic acid, ethyl ester (0.044 mol, 7.6g) in DCM (110ml) under N_2 flow. A solution of 2-naphtalenesulfonyl chloride (0.044 mol) in DCM (50ml) was added dropwise. The mixture was stirred at 10°C for 1 hour and 30 minutes, poured out into ice water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was taken up in diethylether, the precipitate was filtered and dried yielding 13.8g of 4-[(2-naphthalenylsulfonyl)amino]- 1-piperidinecarboxylic acid, ethyl ester, melting point 128°C, intermediate 1.

b) A mixture of interm. 1 (0.072 mol) in HCl 12N (290ml) was stirred and refluxed for 48 hours, then cooled to room temperature, poured out into ice water and basified with NH_4OH. The precipitate was filtered, washed with water, then with diethyl ether and dried, yielding 15.78g (76%) of *N*-4-piperidinyl-2-naphthalenesulfonamide, melting point 172°C, intermediate 2.

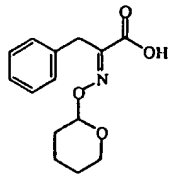
c) NaH 60% (0.0066 mol) was added portionwise at room temperature to a solution of interm. 2 (0.0033 mol) in THF (10ml) under N_2 flow. The mixture was stirred at room temperature for 1 hour, then cooled to 0°C. A solution of 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid, ethyl ester (0.0043 mol) in THF (8ml) was added dropwise quickly. The mixture was stirred at room temperature for 2 hours, poured out into ice water and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1.64g) was crystallized from CH_3OH/diethyl ether. The precipitate was filtered off and dried, yielding 0.925g (63%) of 2-[4-[(2-naphthalenylsulfonyl)amino]-1-piperidinyl]- 5-pyrimidinecarboxylic acid, ethyl ester, intermediate 3.

d) A mixture of interm. 3 (0.0021 mol) and potassium hydroxide (0.0084 mol) in ethanol (20ml) was stirred and refluxed overnight, then cooled to room temperature, poured out into ice water and acidified with HCl 3N. The precipitate was filtered off and dried, yielding 0.66g (76%) of 2-[4-[(2-naphthalenylsulfonyl)amino]-1-piperidinyl]- 5-pyrimidinecarboxylic acid, melting point > 260°C, intermediate 4.

e) TEA (0.0019 mol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodimide hydrochloride (0.0019 mol), 1-hydroxybenzotriazole (0.0019 mol) and O-(tetrahydro-2*H*-pyran-2-yl)-hydroxylamine (0.0019 mol) were added at room temperature to a solution of interm. 4 (0.0014 mol) in DCM/THF 50/50 (20ml) under N_2 flow. The mixture was stirred at room temperature for 24 hours, poured out into ice water. DCM was added. The precipitate was filtered, washed with water and dried, yielding 0.261g (34%) of 2-[4-[(2-naphthalenylsulfonyl)amino]-1-piperidinyl]-*N*-[(tetrahydro-2*H*-pyran-2-yl)oxy]- 5-pyrimidinecarboxamide, melting point 226°C, intermediate 5.

Example A2

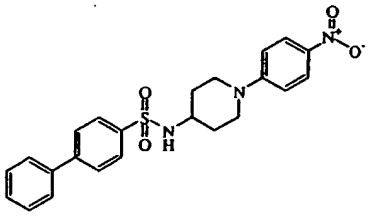
a) Preparation of



intermediate 6

(O-(tetrahydro-2H-pyran-2-yl)- hydroxylamine (0.0085 mol) was added at room temperature to a mixture of α-oxo- benzenepropanoic acid (0.0078 mol) in pyridine (12ml) and EtOH (23ml). The mixture was stirred at room temperature for 1 hour. The solvent was evaporated till dryness. The residue (2.6g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1 70/30/3). The pure fractions were collected and the solvent was evaporated, yielding 1.7g (83%) of intermediate 6.

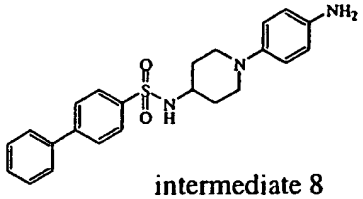
b) Preparation of



intermediate 7

[1,1'-biphenyl]-4-sulfonyl chloride (0.0085 mol) was added at 5°C to a mixture of 1-(4-nitrophenyl)- 4-piperidinamine (0.0071 mol) and TEA (0.0085 mol) in DCM (15ml) under N_2 flow. The mixture was stirred at room temperature for 18 hours. K_2CO_3 10% was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness, yielding 4.1g (>100%) of intermediate 7.

c) Preparation of

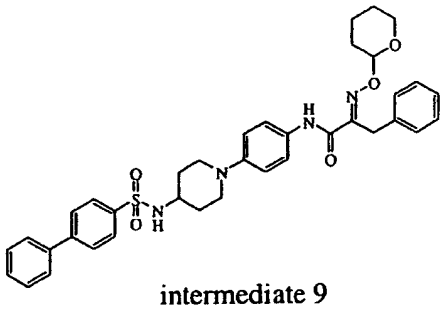


intermediate 8

Titanium chloride (0.0568 mol) was added at room temperature to a mixture of intermediate 7 (0.0071 mol) in THF (140ml). The mixture was stirred at room temperature for 18 hours, poured out on ice, basified with NaOH 3N, extracted with DCM and filtered over celite. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue was taken up in diethyl ether.

The precipitate was filtered off and dried, yielding 0.9g (31%) of intermediate 8, melting point 200°C.

d) Preparation of

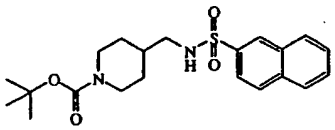


intermediate 9

EDC (0.0012 mol) was added to a mixture of intermediate 8 (0.0009 mol), intermediate 6 (0.0012 mol) and HOBT (0.0012 mol) under N_2 flow. The mixture was stirred at room temperature for 18 hours. K_2CO_3 10% was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (0.94g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98.5/1.5/0.1). The pure fractions were collected and the solvent was evaporated. The residue (0.5g, 78%) was crystallized from CH_3CN/diethyl ether. The precipitate was filtered off and dried, yielding 0.426g (66%) of intermediate 9, melting point 190°C.

Example A3

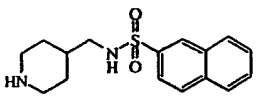
a) Preparation of



intermediate 10

A solution of 2-naphthalenesulfonyl chloride (0.015 mol) in DCM (30ml) was added at 0°C to a solution of 4-(aminomethyl)- 1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (0.014 mol) and TEA (0.022 mol) in DCM (30ml) under N_2 flow. The mixture was stirred at room temperature overnight, poured out into ice water and extracted with DCM. The organic layer was washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 4.8g (84%) of intermediate 10, melting point 148°C.

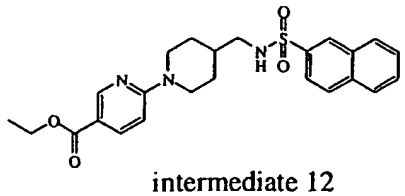
b) Preparation of



intermediate 11

A mixture of intermediate 10 (0.0114 mol) in HCl 3N (50ml) and THF (10ml) was stirred at 80°C for 12 hours, poured out into ice water, basified with NH_4OH and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated, yielding 2.6g (74%) of intermediate 11, melting point 160°C.

c) Preparation of

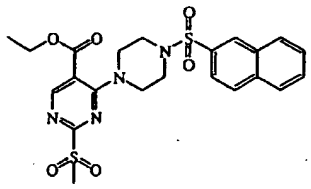


intermediate 12

Sodium hydride 60% (0.0098 mol) was added portionwise at 0°C to a mixture of intermediate 11 (0.0049 mol) in DMF (20ml) under N_2 flow. The mixture was stirred at room temperature for 1 hour. A solution of 6-chloro-3-pyridinecarboxylic acid, ethyl ester (0.0064 mol) in DMF (10ml) was added. The mixture was stirred at 80°C for 12 hours, then cooled, poured out into ice water and stirred at room temperature for 1 hour. The precipitate was filtered, washed with water, then with diethyl ether and dried, yielding 1.2g (54%) of intermediate 12, melting point 172°C.

Example A4

Preparation of

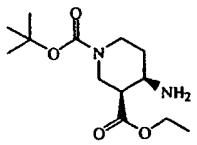


intermediate 13

Sodium hydride 60% (0.015 mol) was added portionwise at room temperature to a mixture of 1-(2-naphthalenylsulfonyl)- piperazine (0.0075 mol) in THF (35ml). The mixture was stirred at room temperature for 1 hour and 30 minutes under N_2 flow. A solution of 4-chloro-2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0098 mol) in THF (35ml) was added dropwise. The mixture was stirred at room temperature for 3 hours and 30 minutes, poured out into ice water and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (4.6g) was purified by column chromatography over silica gel (15-40μm)(eluent: cyclohexane/EtOAc 80/20 to 20/80). The pure fractions were collected and the solvent was evaporated, yielding 0.9g (24%) of intermediate 13, melting point 80°C.

Example A5

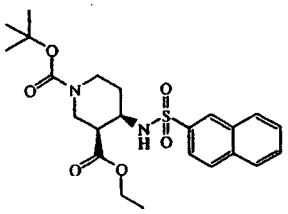
a) Preparation of



CIS
intermediate 14

A mixture of 4-oxo-1,3-piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) 3-ethyl ester (0.02 mol), benzenemethanamine (0.022 mol) and Pd/C (1g) in EtOH (100ml) was hydrogenated at 50°C for 48 hours under a 3 bar pressure, then filtered over celite. The filtrate was evaporated till dryness. The residue (5.9g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 93/7/0.5). The pure fractions were collected and the solvent was evaporated, yielding 2.6g (48%) of intermediate 14 (CIS).

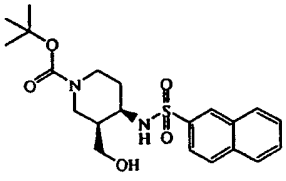
b) Preparation of



CIS
intermediate 15

A solution of 2-naphthalenesulfonyl chloride (0.0105 mol) in DCM (10ml) was added at 5°C to a mixture of intermediate 14 (0.0095 mol) and TEA (0.0134 mol) in DCM (30ml). The mixture was stirred at room temperature overnight, poured out into K_2CO_3 10% and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness, yielding 5.1g (>100%) of intermediate 15 (CIS). This product was used directly in the next reaction step.

c) Preparation of

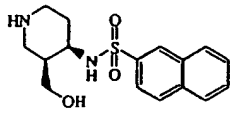


CIS
intermediate 16

A solution of intermediate 15 (0.0089 mol) in THF (40ml) was added dropwise at 5°C to a mixture of tetrahydro-aluminate(1-), lithium (0.0098 mol) in THF (40ml) under N_2 flow. The mixture was stirred for 2 hours. EtOAc then cold water were added. The

mixture was extracted with EtOAc and filtered over celite. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (3.6g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 2.6g (71%) of intermediate 16 (CIS), melting point 190°C.

d) Preparation of

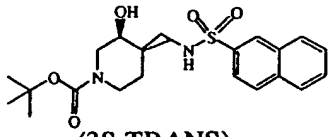


CIS
intermediate 17

A mixture of intermediate 16 (0.0061 mol) in HCl/iPrOH (50ml) was stirred at 50°C for 8 hours. The precipitate was filtered, washed with diethyl ether and dried, yielding 1.6g (73%) of intermediate 17 (CIS), melting point 206°C.

Example A6

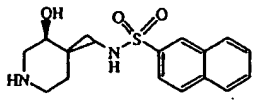
a) Preparation of



(3S-TRANS)
intermediate 18

A solution of 2-naphthalenesulfonyl chloride (0.016 mol) in DCM (40ml) was added dropwise at 0°C to a mixture of 1,1-dimethylethyl (3S-trans)-4-(aminomethyl)-3-hydroxy-1-piperidine carboxylate α-hydroxybenzeneacetate (1:1) (0.013 mol) and TEA (0.04 mol) in DCM (100ml) under N_2 flow. The mixture was brought to room temperature, stirred overnight, poured out into ice water and extracted with DCM. The organic layer was washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.5g) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried. Part (1g) of the residue (4.4g, 80%) was crystallized in hot CH_3CN. The precipitate was filtered, washed with dithyl ether and dried, yielding 0.3g of intermediate 18 (3S-TRANS), melting point 160°C.

b) Preparation of



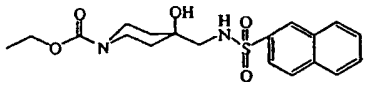
(3S-TRANS)
intermediate 19

HCl./iPrOH (15ml) was added at 0°C to a mixture of intermediate 18 (0.0036 mol) in iPrOH (20ml). The mixture was brought to room temperature, stirred and the solvent was evaporated. Ice and water were added. The organic layer was basified with

NH_4OH. The precipitate was filtered, washed with diethyl ether and dried, yielding 0.9g (78%) of intermediate 19 (3S-TRANS), melting point 200°C.

Example A7

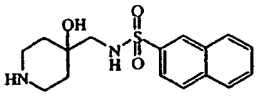
a) Preparation of



intermediate 20

A solution of 2-naphthalenesulfonyl chloride (0.0238 mol) in DCM (40ml) was added dropwise at 0°C to a mixture of 4-(aminomethyl)-4-hydroxy-1-piperidinecarboxylic acid, ethyl ester (0.0198 mol) and TEA (0.036 mol) in DCM (100ml). The mixture was brought to room temperature overnight, poured out into ice water and extracted with DCM. The organic layer was washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (7.6g) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding 6.2g (80%) of intermediate 20, melting point 145°C.

b) Preparation of

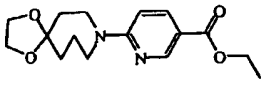


intermediate 21

A mixture of intermediate 20 (0.0076 mol) in HCl 6N (50ml) was stirred and refluxed for 72 hours, then cooled to room temperature and the solvent was evaporated. The mixture was basified with NaOH 3N. EtOAc was added. The mixture was stirred at room temperature overnight. The precipitate was filtered off and dried, yielding 2.5g (100%) of intermediate 21.

Example A8

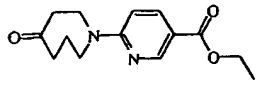
a) Preparation of



intermediate 22

Sodium hydride 60% in oil (0.024 mol) was added portionwise at 5°C to a mixture of 1,4-dioxa-8-azaspiro[4.6]undecane (0.02 mol) in DMF (30ml) under N_2 flow. The mixture was brought to room temperature and stirred for 30 minutes. 6-chloro-3-pyridinecarboxylic acid, ethyl ester (0.024 mol) was added. The mixture was stirred at 90°C for2 hours. Water was added. The mixture was extracted several times with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness, yielding 4.7g (77%) of intermediate 22.

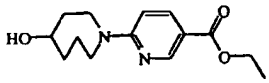
b) Preparation of



intermediate 23

A mixture of intermediate 22 (0.0153 mol) in HCl 3N (45ml) and MeOH (20ml) was stirred and refluxed for 18 hours, poured out on ice, basified with NH_4OH and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (2.3g, 57%)) was purified by column chromatography over silica gel (15-35μm)(eluent: cyclohexane/ EtOAc 60/40). The pure fractions were collected and the solvent was evaporated, yielding 1.1g (27%) of intermediate 23.

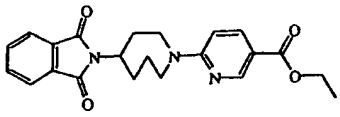
c) Preparation of



intermediate 24

Sodium borohydride (0.0046 mol) was added at 5°C to a mixture of intermediate 23 (0.0041 mol) in MeOH (10ml) under N_2 flow. The mixture was stirred at room temperature for 18 hours. Water was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness, yielding 1.2g (100%) of intermediate 24.

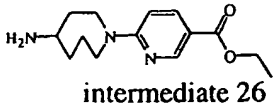
d) Preparation of



intermediate 25

A mixture of intermediate 24 (0.041 mol), 1*H*-isoindole-1,3(2*H*)-dione (0.0054 mol) and triphenyl- phosphine (0.0054 mol) in THF (10ml) was stirred at room temperature under N_2 flow. Diazenedicarboxylic acid, bis(1-methylethyl) ester (0.0054 mol) was added dropwise. The mixture was stirred for 18 hours. K_2CO_3 10% was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (4.6g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40μm). Two fractions were collected and the solvent was evaporated, yielding 0.55g (33%) of intermediate 25.

e) Preparation of

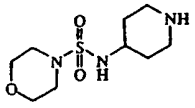


intermediate 26

Hydrazine, monohydrate (0.54ml) was added to a mixture of intermediate 25 (0.0014 mol) in EtOH (6ml). The mixture was stirred and refluxed for 2 hours. Satured NaCl was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated till dryness, yielding 0.4g (>100%) of intermediate 26.

Example A9

Preparation of

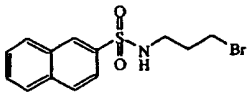


.HCl
intermediate 37

Carbonochloridic acid, 1-chloroethyl ester (0.0088 mol) was added to a mixture of *N*-[1-(phenylmethyl)-4-piperidinyl]- 4-morpholinesulfonamide (0.0055 mol) in 1,2-dichloroethane (20ml). The mixture was stirred and refluxed for 18 hours. The solvent was evaporated till dryness. The residue was taken up in MeOH. The mixture was stirred and refluxed for a week end. The solvent was evaporated till dryness. The residue was crystallized from EtOH/diethyl ether. The precipitate was filtered off and dried, yielding 0.95g (60%) of intermediate 37, melting point 240°C.

Example A10

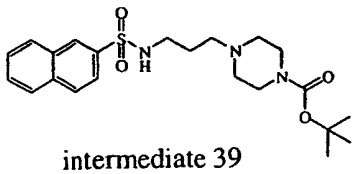
a) Preparation of



intermediate 38

TEA (0.03 mol) then a solution of 2-naphtalenesulfonyl chloride (0.01 mol) in DCM (20ml) were added at 5°C to a solution of 3-bromo-1-propanamine, hydrobromide (0.01 mol) in DCM (25ml) under N_2 flow. The mixture was brought to room temperature, then stirred for 2 hours and the solvent was evaporated at 40°C till dryness, yielding 3.28g (>100%) of intermediate 38.

b) Preparation of

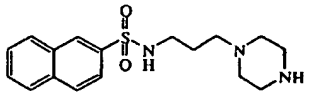


intermediate 39

A mixture of intermediate 38 (0.01 mol), 1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (0.011 mol) and potassium carbonate (0.03 mol) in acetonitrile (40ml) was stirred at room temperature for 18 hours. Water was added. The mixture

was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (5.1g) was purified by column chromatography over silica gel (15-40μm) (eluent: DCM/MeOH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 3.7g (85%) of intermediate 39.

c) Preparation of

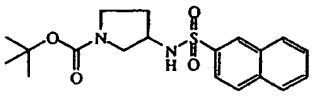


.HCl
intermediate 40

HCl 3N (35ml) was added to a mixture of intermediate 39 (0.0083 mol) in THF (10ml). The mixture was stirred at room temperature for 18 hours. The solvent was evaporated till dryness. The residue was taken up in EtOH. The solvent was evaporated till dryness. The residue was taken up in diethyl ether. The precipitate was filtered off and dried, yielding 2.8g (91%) of intermediate 40 .HCl, melting point:190°C.

Example A11

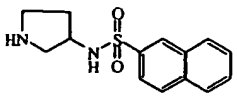
a) Preparation of



intermediate 41

A solution of 2-naphthalenesulfonyl chloride (0.043 mol) in DCM (50ml) was added at 10°C to a solution of 3-amino-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (0.041 mol) and TEA (0.0615 mol) in DCM (200ml) under N_2 flow. The mixture was stirred at room temperature for 4 hours, then poured out into ice water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (46g) was purified by column chromatography over silica gel (20-45μm) (eluent: DCM/EtOAc 90/10 to DCM/MeOH 95/5). The pure fractions were collected and the solvent was evaporated, yielding 18g (>100%) of intermediate 41.

b) Preparation of

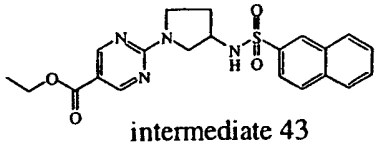


intermediate 42

A mixture of intermediate 41 (0.046 mol) in HCl 3N (180ml) and THF (45ml) was stirred at 80°C overnight, then cooled to room temperature, poured out into ice water, basified with NH_4OH and extracted with DCM. The organic layer was separated, dried

($MgSO_4$), filtered, and the solvent was evaporated. The residue (17g) was crystallized from DIPE. The precipitate was filtered off and dried, yielding 9.33g (73%) of intermediate 42, melting point 158°C.

c) Preparation of

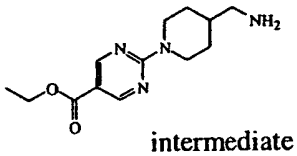


intermediate 43

A solution of 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0195 mol) in acetonitrile (40ml) was added dropwise at 10°C to a solution of intermediate 42 (0.015 mol) and potassium carbonate (0.03 mol) in acetonitrile (100ml). The mixture was stirred at room temperature for 1 hour and 30 minutes, poured out into ice water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (7.64g) was crystallized from CH_3CN/diethyl ether. The precipitate was filtered, washed with diethyl ether and dried, yielding 2.21g (35%) of intermediate 43, melting point: 180°C.

Example A12

Preparation of

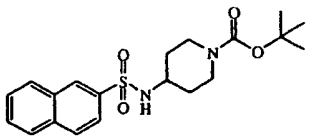


intermediate 44

A solution of 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0434 mol) in acetonitrile (100ml) was added dropwise at 10°C to a solution of 4-piperidinemethanamine (0.0868 mol) and potassium carbonate (0.0434 mol) in acetonitrile (200ml) under N_2 flow. The mixture was stirred at room temperature for 2 hours, poured out into ice water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (14.18g) was purified by column chromatography over silica gel (20-45μm) (eluent: DCM/MeOH/NH_4OH 90/10/1 to 80/20/2). The pure fractions were collected and the solvent was evaporated, yielding 3.7g (32%) of intermediate 44.

Example A13

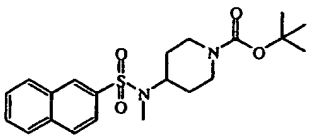
a) Preparation of



intermediate 45

A mixture of 4-amino-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (0.025 mol) and TEA (0.035 mol) in DCM (30ml) was stirred at 5°C under N_2 flow. A solution of 2-naphthalenesulfonyl chloride (0.0275 mol) in DCM (20ml) was added. The mixture was stirred at room temperature for 18 hours. Water was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (11.6g) was purified by column chromatography over silica gel (20-45μm) (eluent: DCM/MeOH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 7.5g (77%) of intermediate 45.

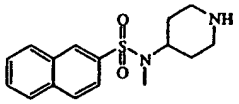
b) Preparation of



intermediate 46

Sodium hydride 60% in oil (0.0033 mol) was added portionwise at room temperature to a mixture of intermediate 45 (0.0028 mol) in DMF (15ml) under N_2 flow. The mixture was stirred for 1 hour. Iodomethane (0.0033 mol) was added. The mixture was stirred at 80°C for 3 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (1.24g) was dissolved in acetonitrile. The mixture was crystallized from DIPE. The precipitate was filtered off and dried, yielding 0.64g (56%) of intermediate 46, melting point 130°C.

c) Preparation of

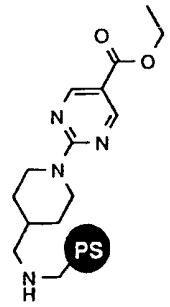


intermediate 47

Trifluoro acetic acid (1.5ml) was added to a mixture of intermediate 46 (0.0015 mol) in DCM (15ml). The mixture was stirred at room temperature for 48 hours, poured out into ice and NH_4OH and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness, yielding 0.474g (100%) of intermediate 47.

Example A14

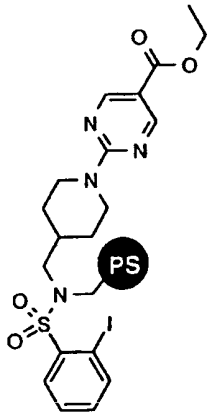
a) Preparation of



intermediate 48

2-(3,5-Dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (1 mmol, 0.66 mmol/g, 1.515g, NovaBiochem, Cat. Nr. 01-64-0261), intermediate 44 (1 mmol) and titatium(IV)isopropoxide (5 mmol) were dissolved in DCM (25 ml) and the suspension was shaken for 1 hour. Then, sodium acetoxy borohydride (5 mmol) was added and the resulting reaction mixture was shaken overnight at ambient temperature. The resin was filtered off and washed twice with DCM (10 ml) and twice with MeOH (10 ml), then once with DCM with 2% (v/v) diisopropylethylamine (10 ml) and finally twice with DCM (10 ml). The resin was dried in vacuo at 50°C for 2 hours yielding 1.825 g (quant.) of intermediate 48.

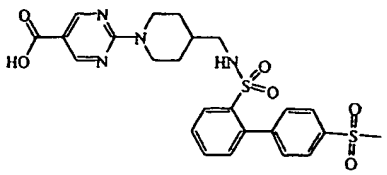
b) Preparation of



intermediate 49

To a cooled (0°C, ice bath) and stirred suspension of intermediate 48 (1 mmol and TEA (1.5 mmol) in DCM (25 ml) was slowly added a solution of 2-iodo-benzenesulfonyl chloride (1.5 mmol, 454 mg)) in DCM (10 mL). The suspension was allowed to warm up to room temperature and was stirred for another 2 hours. Then, the resin was filtered off and washed twice with DCM (10 mL) and twice with MeOH (10 mL) and then once more with DCM (10 mL). The resin was dried in vacuo at 50°C for 2 hours, yielding 2.0675 g (quant.) of intermediate 49.

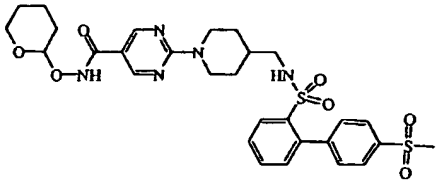
c) Preparation of



intermediate 50

Intermediate 49 was divided up in portions of 0.1 mmol, each in a separate tube of a Bohdan Miniblock™ (supplier: Mettler Toledo Autochem) and [4-(methylsulfonyl)phenyl]- boronic acid (0.8 mmol) dissolved in 1,4-dioxane (2 mL) and aqueous NaOH, 2 M (1.6 mmol) were added. The mixtures were shaken under a nitrogen atmosphere for 30 minutes. Next, $PdCl_2(PPh_3)_2$ (0.02 mmol,) dissolved in NMP (0.5 ml), was added and the mixture was shaken overnight at 80°C. The system was allowed to cool down to room temperature and the resin was filtered off, washed with DMF (3 x 2 mL), water (3 x 2 mL), DMF (3 x 2 mL), MeOH (3 x 2 mL), DCM (3 x 2 mL). Then a mixture of trifluoroacetic acid/dichloromethane/triisopropylsilane 49/49/2 (6 mL) was added to each vessel and the Bohdan Miniblock™ was shaken for 2 hours at room temperature. The mixtures were filtered off, the resin was washed with DCM (2 mL), and the filtrate concentrated. The product was then treated with a mixture of THF (1 mL) and aqueous NaOH (1 mL, 1N) for 48 hours at room temperature. Finally, the mixture was neutralized by the addition of aqueous HCl (1 mL, 1N), and dried at 70°C under a nitrogen flow, yielding intermediate 50.

d) Preparation of



intermediate 51

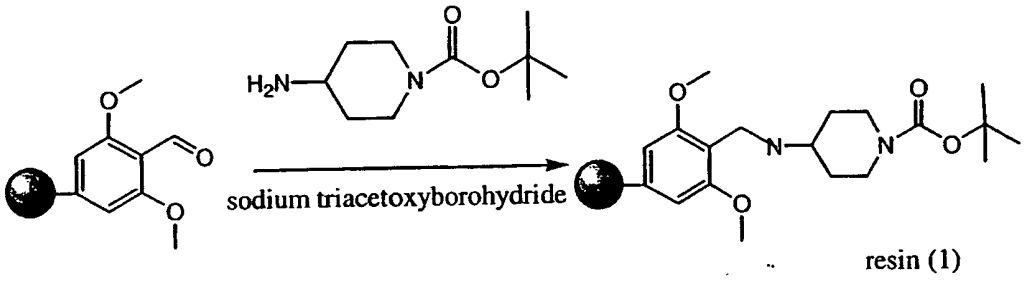
To intermediate 50 (0.1 mmol) was subsequently added HOBT (0.13 mmol) dissolved in dry THF (1 mL), EDCI (0.13 mmol), dissolved in dry THF (1ml), and TEA (0.15 mmol). The mixture was shaken at room temperature for 10 minutes. Then, tetrahydropyran-O-protected hydroxylamine (0.13 mmol) dissolved in dry THF (1ml) was added and the reaction mixture was shaken at room temperature overnight. The solvents were evaporated and the product was purified using normal phase HPLC , yielding intermediate 51.

B. Preparation of the final compounds

Example B1

a) Preparation of resin (1):

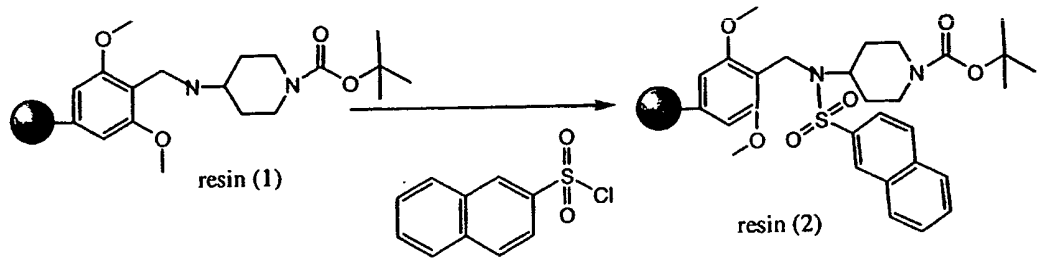
A mixture of Novabiochem 01-64-0261 commercial resin (200mg, loading: 0,94 mmol/g), mono N-Boc-4-aminopiperidine (188 mg) and titanium (IV) isopropoxide ($Ti(OiOr)_4$ (277μl) in DCM (4 ml) was shaken gently for 90 minutes at room temperature. Sodium triacetoxyborohydride (199 mg) was added and the reaction mixture was shaken gently overnight at room temperature , then the resin was filtered, washed once with DCM, once with MeOH, then two times with DCM/DIEA 10%, washed three times with firstly DCM, followed secondly by three times methanol, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH. This gave a resin identified as resin (1), which is used in the next reaction step without further purification.



resin (1)

b) Preparation of resin (2):

The resin (1) was washed three times with DCM. To resin (1) was added 2-naphtalenesulfonyl chloride (215 mg) in 4 ml DCM and DIEA (307 μl), the resin was shaken gently overnight, the resin was filtered, washed with 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH. This gave resin (2), which is used in the next reaction step without further purification.

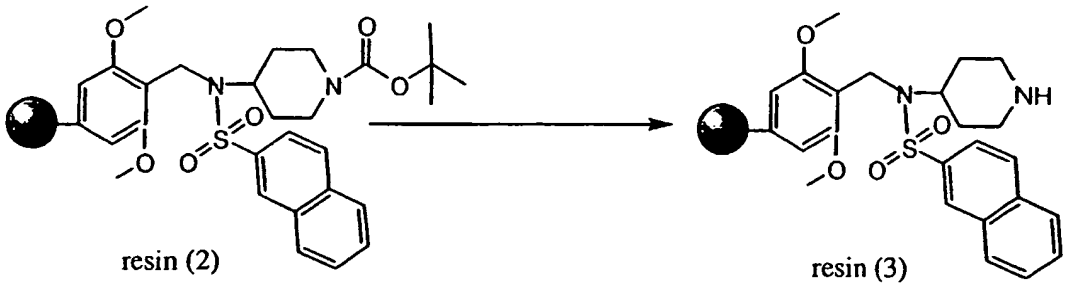


resin (1) resin (2)

c) Preparation of resin (3):

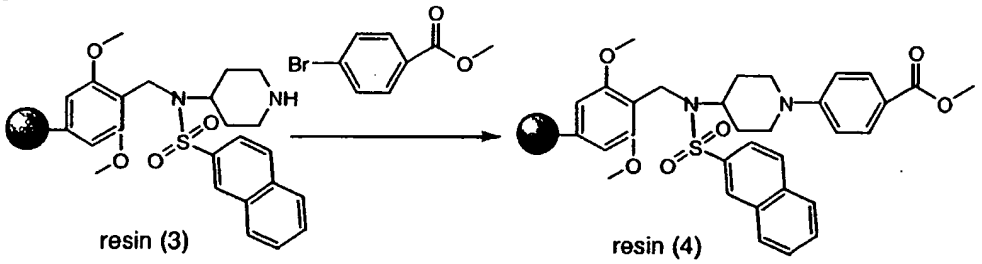
The resin (2) was washed three times with DCM. To resin (2) was added 4 ml TMSOTf – 2,6-lutidine (1M/1,5M) in DCM, the resin was shaken gently for 3 h at room

temperature, the resin was filtered, washed with 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH. This gave resin (3), which is used in the next reaction step without further purification.



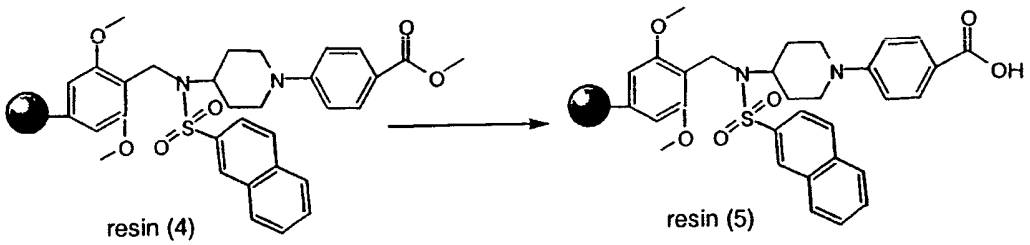
d) Preparation of resin (4):

The resin (3) was washed three times with toluene.To resin (3) was added 4-bromo methylbenzoate (606 mg) in 3 ml toluene and BINAP (117 mg) and Cs_2CO_3 (326 mg), the resin was shaken gently for 45 min at room temperature under nitrogen. $Pd(OAc)_2$ in 1 ml toluene was added to the reaction mixture. The resin was shaken gently for 18 h at 110°C under nitrogen. The resin was filtered warm, the resin was washed 3x with DMF at 80°C, 3x with H_2O at 80°C, 3x with DMF at 80°C, washed 3x with DMF at room temperature, 3x with H_2O, 3x with DMF, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM. This gave resin (4), which is used in the next reaction step without further purification.



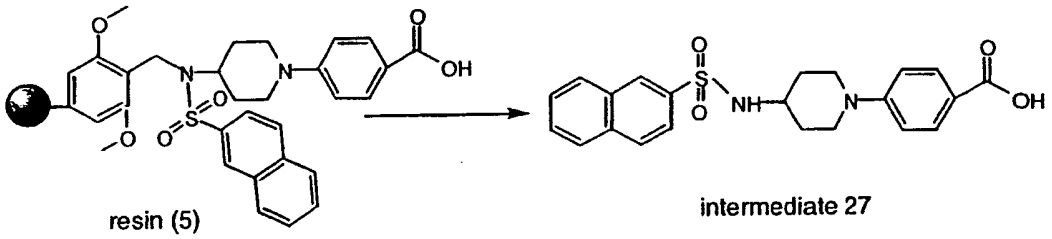
e) Preparation of resin (5):

The resin (4) was washed three times with NMP. To resin (4) was added potassium trimethylsilanolate ($KOSiMe_3$) (240 mg) in 4 ml NMP, the resin was shaken gently for 24 h at 50°C, the resin was filtered, washed with 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH. This gave resin (5), which is used in the next reaction step without further purification.



f) Preparation of intermediate 27:

The resin (5) was washed three times with DCM. To resin (5) was added 5 ml TFA/TIS/DCM (5:2:93), the resin was shaken gently for 2h at room temperature, the resin was filtered, washed with DCM. The filtrate was blown dry under nitrogen at 50°C, DCM (2 ml) was added and blown dry under nitrogen at 50°C, DCM (2 ml) was added and blow dry under nitrogen at 50°C. This gave the free carboxylic acid (intermediate 27) as TFA-salt yielding 66 mg.



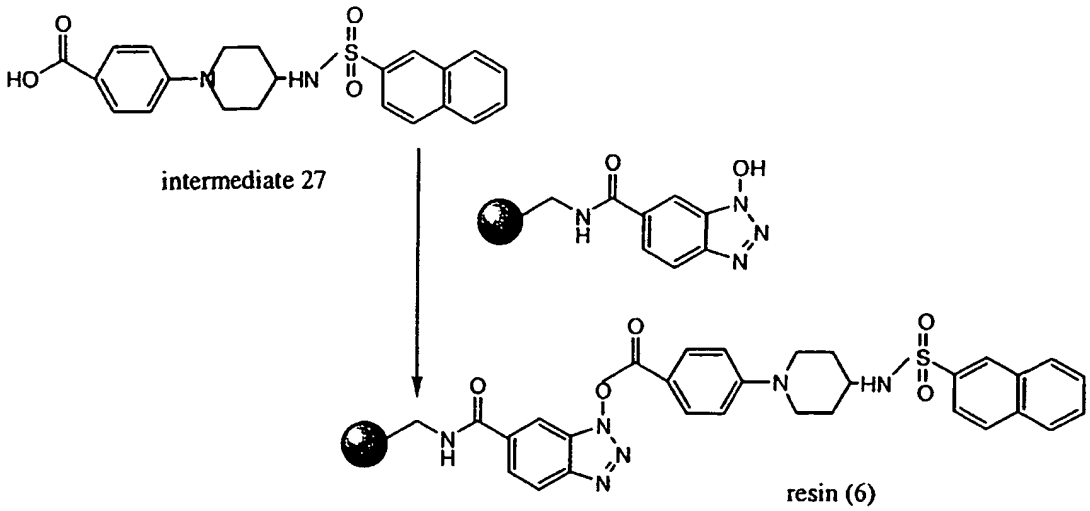
g) Preparation of resin (6) method A:

Intermediate 27 was concentrated at 50°C under nitrogen with thionyl chloride ($SOCl_2$) (1 ml), DCM (2 ml) was added and blown dry under nitrogen at 50°C, DCM (2 ml) was added and blown dry under nitrogen at 50°C. DCM (3 ml) was added and the solution was added to a commercial resin of Novabiochem 01-64-0425 (300 mg, loading: 1,3 mmol/g), to the mixture was added 1 ml of 2,6-lutidine and 1 ml DCM. The resin was shaken gently for 1 h, the resin was filtered, washed with 3xDMF, 3xDCM, 3xDMF. This gave resin (7), which is used in the next reaction step without further purification.

h) Preparation of resin (6) method B:

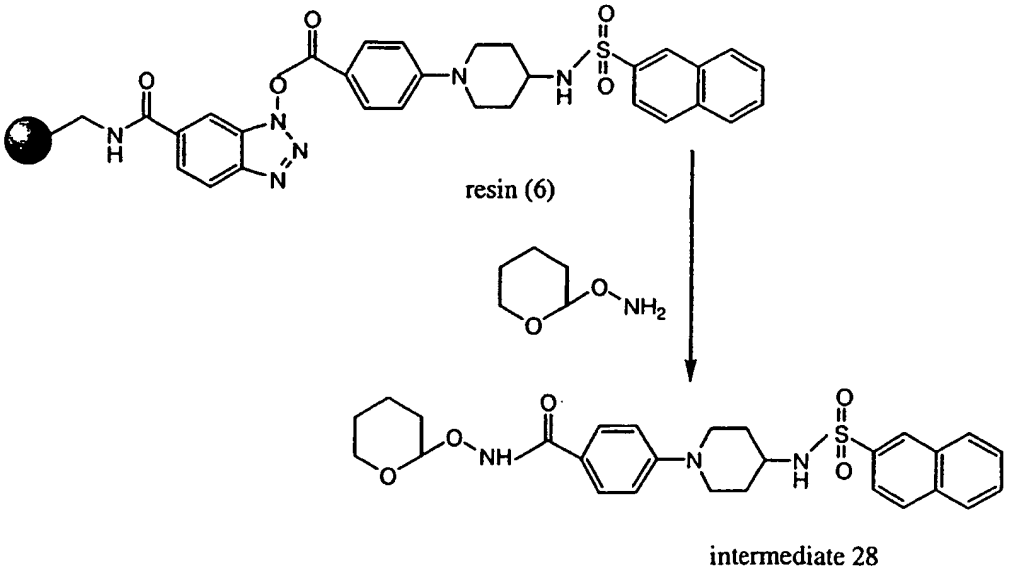
Intermediate 27 was treated with DCM, NEt_3 and H_2O and a few drops of MeOH, This was dried over extrelute 3N and blow dry under nitrogen at 50°C. DCM (3 ml) was added 3 times and blown dry under nitrogen at 50°C. The free base was dissolved in DCM/DMF 4ml/1ml and the solution was added to a commercial resin of Novabiochem 01-64-0425 (300 mg, loading: 1,3 mmol/g), to the mixture was added DMAP (10 mg).The resin was shaken gently for 15 min at room temperature, DIPCDI (70μl) was added. The resin was shaken gently for 4 h at room temperature, the resin

was filtered, washed with 3xDMF, 3xDCM, 3xDMF. This gave resin (7), which is used in the next reaction step without further purification.



i) Preparation of intermediate 28:

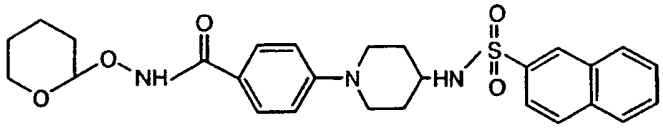
To resin (6) was added O-(tetrahydr-2H-pyran-yl)-hydroxylamine (60 mg) in 4 ml DCM, the resin was shaken gently for 18 h at room temperature, the resin was filtered washed with DCM (2 ml), filtered and blow dry under nitrogen at 50°C. This gave intermediate 28 yielding 32 mg.



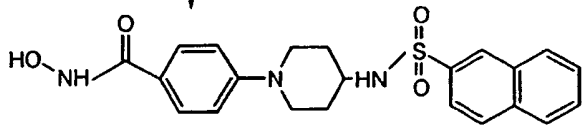
j) Preparation of compound 1:

Intermediate 28 was stirred overnight in 5 % TFA in MeOH (5 ml), the reaction mixture was poured into 4 ml H_2O and $NaHCO_3$ (300 mg), the product was extracted with DCM (5 ml) two times, the DCM layer was dried over $MgSO_4$, filtered and blown dry under nitrogen at 50°C. This gave final compound 1, yielding 10 mg.

Remark: THP-protected pyridine hydroxamic acid was deprotected 2x.
Sometimes compound 1 was suspended in DIPE to remove THP-ONH_2

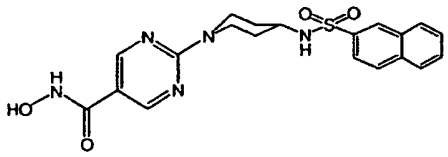


intermediate 28



Compound 1

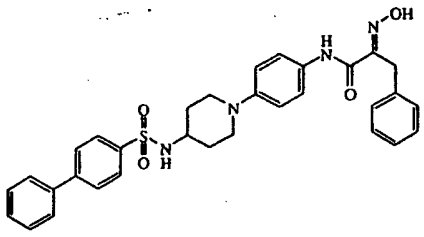
Example B2
Preparation of



compound 2

TFA (4ml) was added at 0°C to a solution of interm. 5 (0.0004 mol) in MeOH (20ml) and DCM (20ml). The mixture was stirred at room temperature for 48 hours. The solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.137g (72%) of compound 2, melting point 200°C.

Example B3
Preparation of

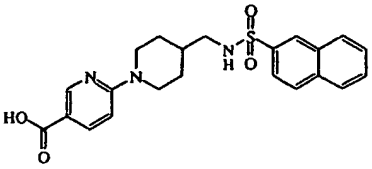


compound 3

Methanesulfonic acid (0.25ml) was added at room temperature to a mixture of intermediate 9 (0.0003 mol) in MeOH (3ml). The mixture was stirred at room temperature for 18 hours. Methanesulfonic acid (0.25 ml) was added. The mixture was stirred at room temperature for 18 hours. Ice was added. The mixture was basified with K_2CO_3 10% and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.21g, 100%) was crystallized from DCM/MeOH. The precipitate was filtered off and dried, yielding: 0.155g (71%) of compound 3, melting point 262°C.

Example B4

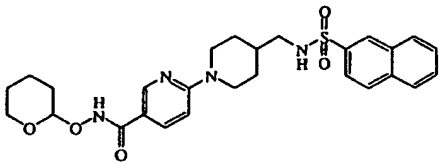
Preparation of



Sodium salt
intermediate 29

a) A mixture of intermediate 12 (0.0024 mol) and NaOH (0.0048 mol) in EtOH (60ml) was stirred and refluxed for 48 hours, then cooled. The precipitate was filtered, washed with EtOH, then with diethyl ether and dried, yielding 0.95g (89%) of intermediate 29 (.Na) .

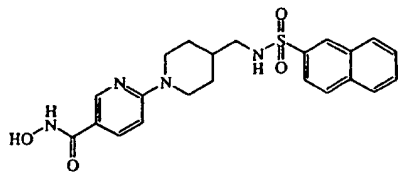
Preparation of



intermediate 30

b) O-(tetrahydro-2*H*-pyran-2-yl)- hyroxylamine (0.0028 mol) then a solution of EDC (0.0028 mol) in DCM (20ml), then a solution of HOBT (0.0028 mol) in THF (20ml) were added at room temperature to a mixture of intermediate 29 (0.0021 mol) in DCM (10ml) and THF (10ml). The mixture was stirred at room temperature for 12 hours, poured out into water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1). The pure fractions were collected and the solvent was evaporated. The residue (0.38g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.2g of intermediate 30, melting point 138°C.

Preparation of

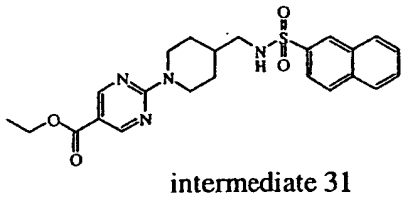


compound 4

c) Trifluoroacetic acid (1ml) was added at 0°C to a mixture of intermediate 30 (0.0009 mol) in MeOH (15ml). The mixture was stirred at room temperature for 72 hours. The solvent was evaporated. The residue was taken up in CH_3CN/diethyl ether. The precipitate was filtered off and dried, yielding 0.29g (69%) of compound 4, melting point 173°C.

Example B5

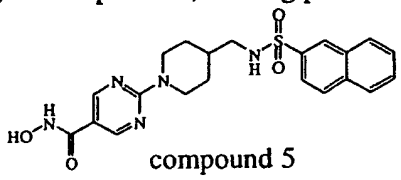
Preparation of



intermediate 31

NaH (0.005 mol) was added at 0°C to a solution of intermediate 11 (0.0033 mol) in THF (20ml) under N_2 flow. The mixture was stirred at 0°C for 1 hour. A solution of 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid, , ethyl ester (0.0043 mol) in THF (10ml) was added. The mixture was stirred at 0°C for 2 hours, poured out into ice water and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1.4g) was purified by column chromatography over silica gel (15-35μm)(eluent: cyclohexane/EtOAc 70/30). The pure fractions were collected and the solvent was evaporated. The residue (0.94g, 63%) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.65g of intermediate 31, melting point 186°C .

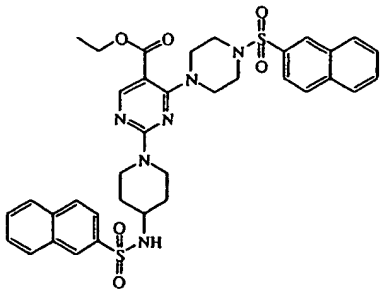
Intermediate 31 was handled analogously as described in example [B4] to give 0.246 (77% of the last step) of compound 5, melting point 262°C .



compound 5

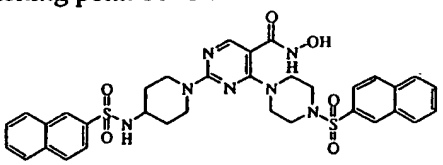
Example B6

Preparation of



intermediate 32

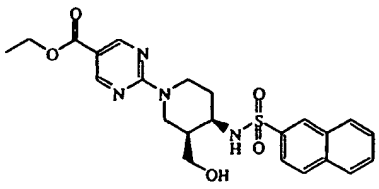
Sodium hydride 60% (0.0006 mol) was added portionwise at room temperature to a solution of *N*-4-piperidinyl- benzenesulfonamide, monohydrochloride (0.0004 mol) in THF (4ml) under N_2 flow. The mixture was stirred at room temperature for 1 hour and 30 minutes. A solution of intermediate 13 (0.0004 mol) in THF (4ml) was added dropwise. The mixture was stirred at room temperature for 2 hours, poured out into ice water and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.68g) was purified by column chromatography over silicagel (10μm)(eluent: DCM 100). The pure fractions were collected and the solvent was evaporated. The residue (0.376g) was purified by column chromatography over silicagel (10μm)(eluent: cyclohexane/EtOAc 70/30). Two fractions were collected and the solvent was evaporated. The residue was dried several times with diethyl ether, yielding 0.208g (36%) of intermediate 32 .
Intermediate 32 was handled analogously as described in example [B4] to give 0.03g (50%) of compound 6, melting point 80°C .



trifluoroacetate (1:1)
compound 6

Example B7

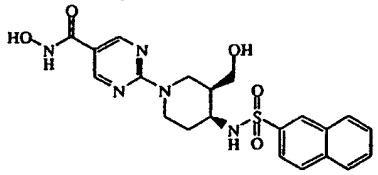
Preparation of



CIS
intermediate 33

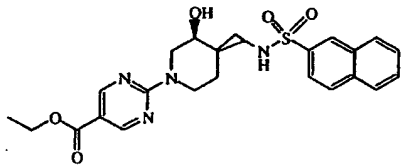
A mixture of intermediate 17 (0.0024 mol), 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid, ethyl ester (0.0032 mol) and K_2CO_3 (0.0074 mol) in acetonitrile (15ml) was

stirred at 90°C for 8 hours, poured out into water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.63g) was purified by column chromatography over silicagel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.1). The pure fractions were collected and the solvent was evaporated. The residue (0.75g, 64%) was crystallized from CH_3CN/diethyl ether/DIPE. The precipitate was filtered off and dried, yielding 0.5g (43%) of intermediate 33 (CIS), melting point 155°C.
Intermediate 33 was handled analogously as described in example [B4] to give 0.16g (75%) of compound 7 (CIS), melting point 203°C.



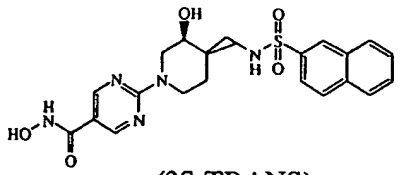
(CIS)
compound 7

Example B8
Preparation of



(3S-TRANS)
intermediate 34

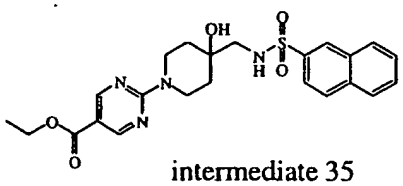
A mixture of intermediate 19 (0.0028 mol), 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid, ethyl ester (0.0034 mol) and K_2CO_3 (0.0056 mol) in acetonitrile (40ml) was stirred at room temperature for 12 hours, poured out into water and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.3g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.1). The pure fractions were collected and the solvent was evaporated. The residue (0.91g, 68%) was crystallized from acetonitrile. The precipitate was filtered off and dried, yielding 0.45g of intermediate 34 (3S-TRANS), melting point 130°C.
Intermediate 34 was handled analogously as described in example [B4] to give 0.09g (53%) of compound 8 (3S-TRANS), melting point 224°C.



(3S-TRANS)
compound 8

Example B9

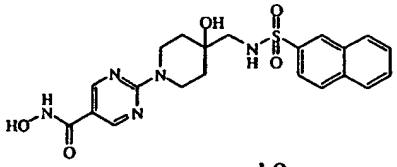
Preparation of



intermediate 35

A mixture of intermediate 21 (0.0056 mol), 2-(methylsulfonyl)-5-pyrimidinecarboxylic acid, ethyl ester (0.0073 mol) and K_2CO_3 (0.0112 mol) in acetonitrile (80ml) was stirred at room temperature overnight, poured out into ice water and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1). The pure fractions were collected and the solvent was evaporated. The residue(0.4g, 15%) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.28g of intermediate 35, melting point 208°C.

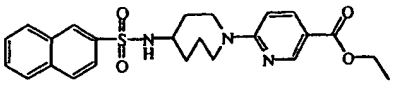
Intermediate 35 was handled analogously as described in example [B4] to give 0.125g of compound 9, melting point 228°C.



compound 9

Example B10

Preparation of

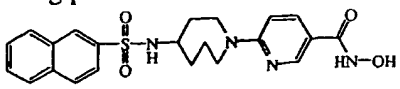


intermediate 36

A solution of 2-naphthalenesulfonyl chloride (0.0043 mol) in DCM (10ml) was added at room temperature to a mixture of intermediate 26 (0.0036 mol) and TEA (0.005 mol) in DCM (10ml) under N_2 flow. The mixture was stirred at room temperature for 18 hours. Water was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The

residue (1.69g) was purified by column chromatography over silica gel (15-40μm)(eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.1). The pure fractions were collected and the solvent was evaporated, yielding 1g (61%) of intermediate 36.

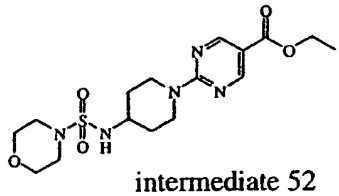
Intermediate 36 was handled analogously as described in example [B4] to give 0.7g (93%) of compound 10, melting point 142°C.



trifluoroacetate (1:1)
compound 10

Example B11

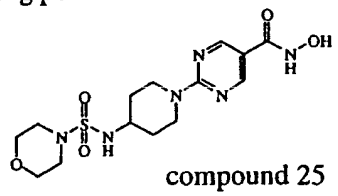
Preparation of



intermediate 52

A mixture of intermediate 37(0.0017 mol), 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0022 mol) and potassium carbonate (0.0052 mol) in acetonitrile (10ml) was stirred at room temperature for 2 hours. Water was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (0.78g) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.426g (61%) of intermediate 52, melting point 135°C.

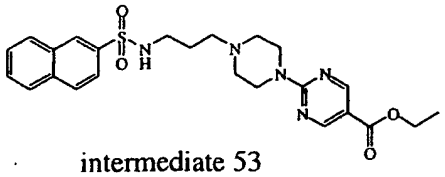
Intermediate 52 was handled analogously as described in example [B4] to give 0.064g (78%) of compound 25, melting point 217°C.



compound 25

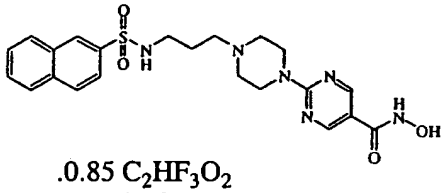
Example B12

Preparation of



intermediate 53

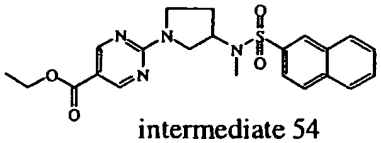
A mixture of intermediate 40 (0.0027 mol), 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0035 mol) and potassium carbonate (0.0081 mol) in acetonitrile (10ml) was stirred at room temperature for 18 hours. Water was added. The precipitate was filtered, washed with water, then with diethyl ether and dried, yielding 0.96g (74%) of intermediate 53, melting point 132°C.
Intermediate 53 was handled analogously as described in example [B4] to give 0.106g (59%) of compound 26, melting point 115°C.



.0.85 $C_2HF_3O_2$
.1.11 H_2O
compound 26

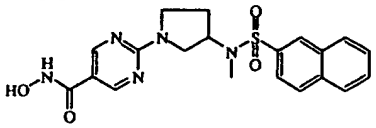
Example B13

Preparation of



intermediate 54

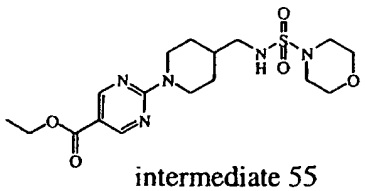
Sodium hydride (0.0017 mol) was added at room temperature to a solution of intermediate 43 (0.0008 mol) in DMF (5ml) under N_2 flow. The mixture was stirred for 30 minutes. Iodomethane (0.0013 mol) was added. The mixture was stirred at room temperature for 1 hour, poured out into ice water and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), filtered, and the solvent was evaporated, yielding 0.38g (100%) of intermediate 54.
Intermediate 54 was handled analogously as described in example [B4] to give 0.155g (73%) of compound 27, melting point 158°C.



. 0.51 $C_2HF_3O_2$
compound 27

Example B14

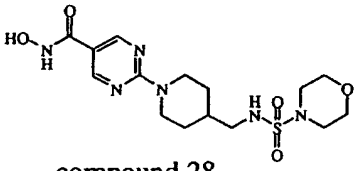
Preparation of



intermediate 55

A solution of 4-morpholinesulfonyl chloride (0.0061 mol) in 1,2-dichloro ethane (3ml) was added dropwise at room temperature to a solution of intermediate 44 (0.0061 mol) and TEA (0.0122 mol) in 1,2-dichloro ethane (7ml). The mixture was stirred at room temperature for 24 hours, poured out into ice water and extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from MeOH/diethyl ether. The precipitate was filtered, washed with diethyl ether and dried, yielding 1.245g (49%) of intermediate 55, melting point 189°C.

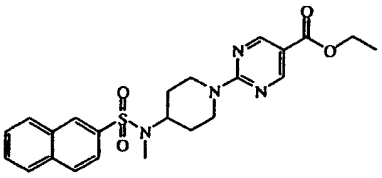
Intermediate 55 was handled analogously as described in example [B4] to give 0.449g (83%) of compound 28, melting point 217°C.



compound 28

Example B15

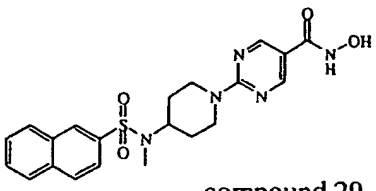
Preparation of



intermediate 56

A mixture of intermediate 47(0.0015 mol), 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0018 mol) and potassium carbonate (0.0045 mol) in acetonitrile (10ml) was stirred at room temperature for 18 hours. Water was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (0.78g) was crystallized from DIPE/diethyl ether. The precipitate was filtered off and dried, yielding 0.42g (61%) of intermediate 56, melting point: 143°C.

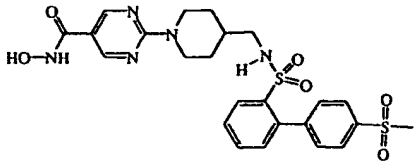
Intermediate 56 was handled analogously as described in example [B4] to give 0.2g (75%) of compound 29, melting point >260°C.



compound 29

Example B16

Preparation of

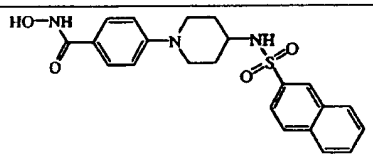
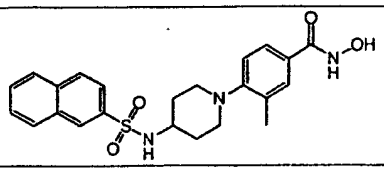
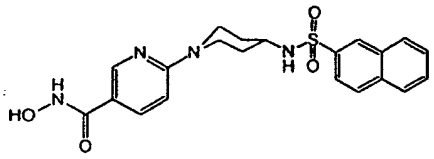
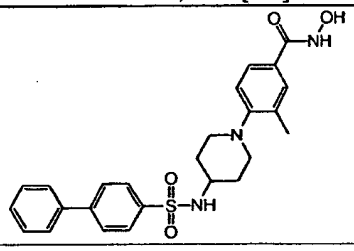
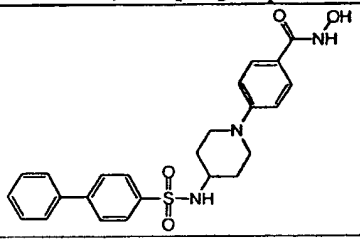
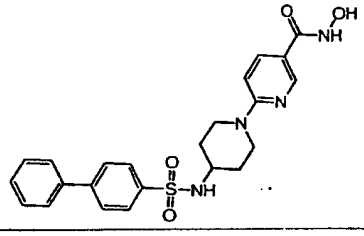
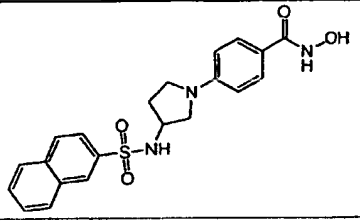
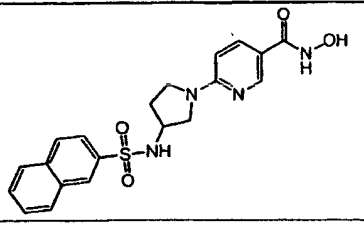
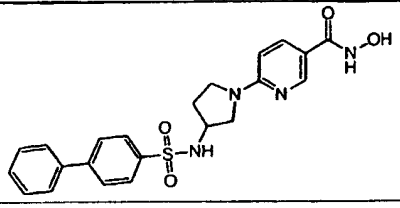


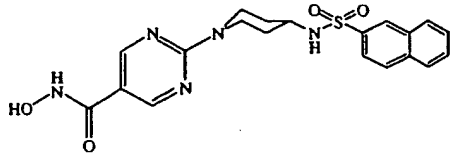
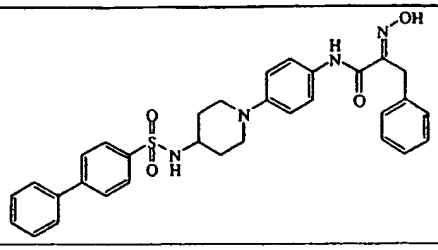
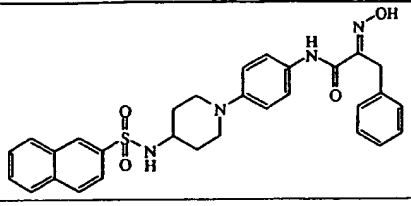
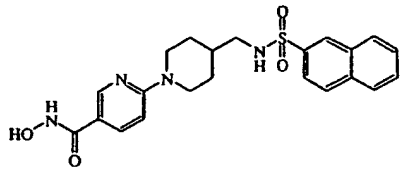
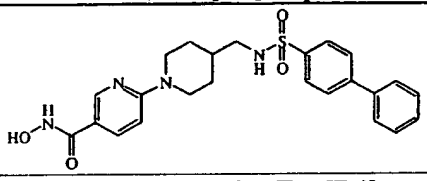
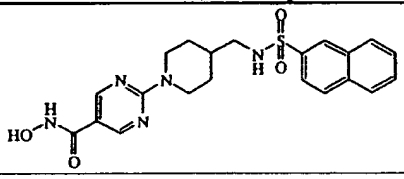
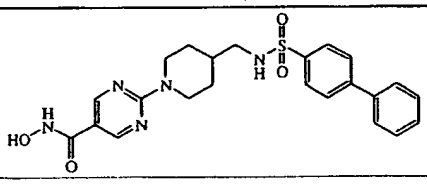
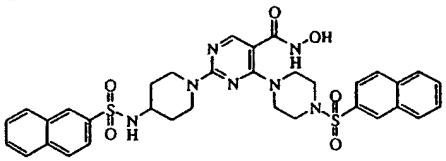
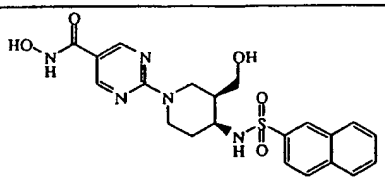
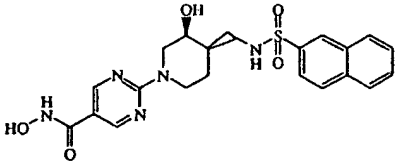
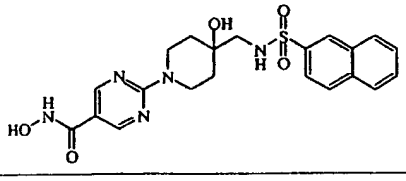
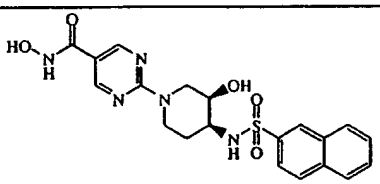
compound 30

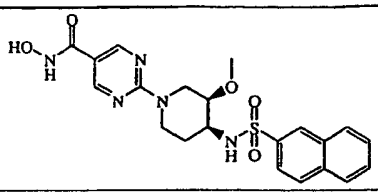
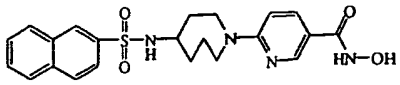
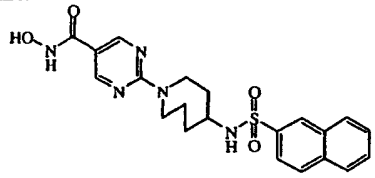
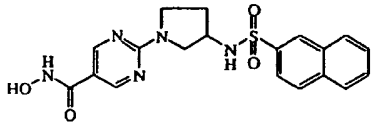
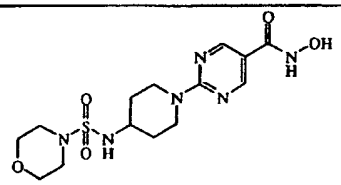
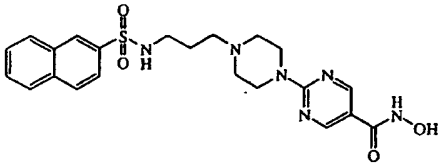
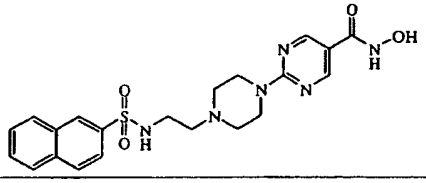
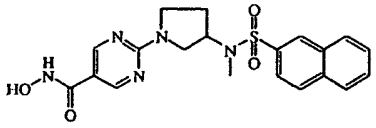
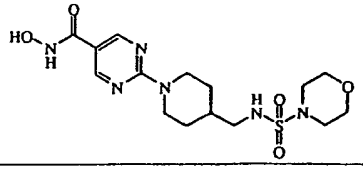
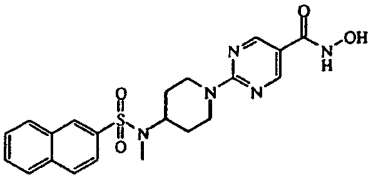
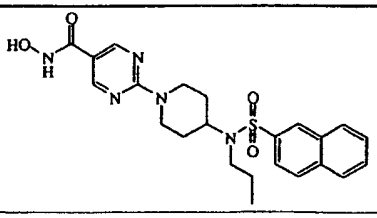
Intermediate 51was treated with a 5% trifluoroacetic acid solution in a mixture of DCM/MeOH (1/1, 2ml) for 7 days. The solvents were evaporated at room temperature under a flow of nitrogen and the resulting oils were treated for a second time with a 5% trifluoroacetic acid solution in a mixture of DCM/MeOH (1/1, 2ml). The resulting reaction mixture was shaken for another 7 days. The solvents were then evaporated at room temperature under a flow of nitrogen, followed by addition of 1,4-dioxane and repeating the concentration procedure. Then, the samples were dried under a nitrogen flow overnight at 40°C to establish complete deprotection, yielding 7mg of compound 30.

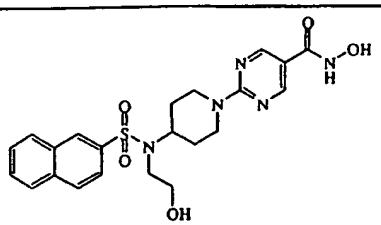
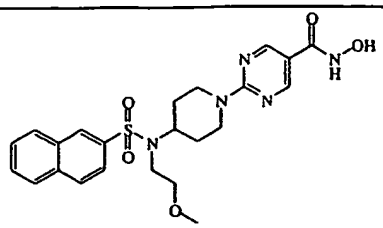
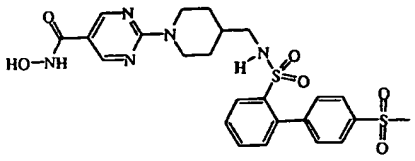
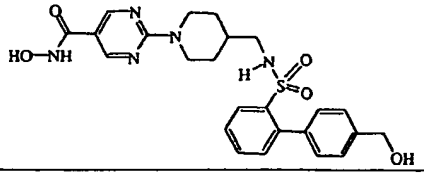
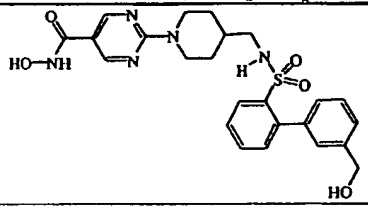
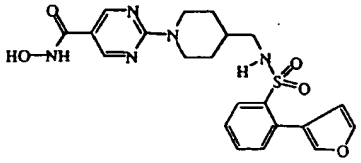
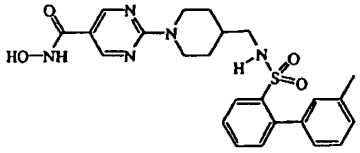
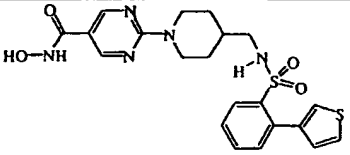
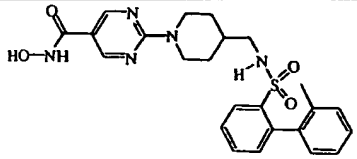
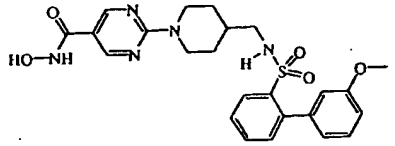
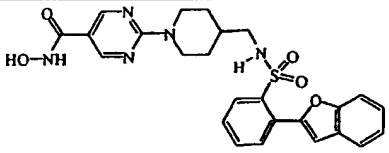
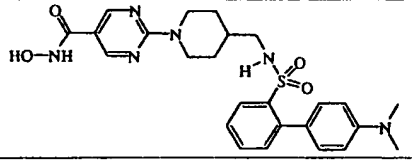
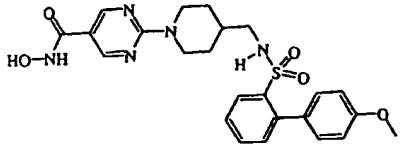
Table F-1 lists the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables : .$C_2HF_3O_2$ stands for the trifluoroacetate salt, Co.No. stands for Compound Number, Ex. [Bn°] refers to the same method as described in the Bn° examples. Some compounds have been characterized via melting point (mp.).

Table F-1

	
Co. No.1; Ex. [B1]	Co. No.11; Ex. [B1]
	
Co. No.12; Ex. [B1]; mp. 163°C	Co. No.13; Ex. [B1]
	
Co. No.14; Ex. [B1]	Co. No.15; Ex. [B1]
	
Co. No.16; Ex. [B1]	Co. No.17; Ex. [B1]
	
Co. No.18; Ex. [B1]	

	
Co. No.2; Ex. [B2], mp. 200°C	Co. No. 3; Ex [B3]; mp. 262°C
	
Co. No.19; Ex. [B3]; mp. 255°C	Co. No.4; Ex. [B4]; mp. 173°C
	
$C_2HF_3O_2$, Co. No.20; Ex. [B4]; mp. 220°C	Co. No. 5; Ex. [B5]; mp. 262°C
	
.0.7 CH_3OH; Co. No.21; Ex. [B5]; mp. 284°C	$C_2HF_3O_2$; Co. No.6; Ex. [B6]; mp. 80°C
	
(CIS); Co. No.7; Ex. [B7]; mp. 203°C	(3S-TRANS); Co. No.8; Ex. [B8]; mp. 224°C
	
Co. No.9; Ex. [B9]; mp. 228°C	CIS, Co. No.22; Ex. [B9]; mp. 245°C

	
(B-CIS); Co. No.23; Ex. [B9]; mp. 210°C	$C_2HF_3O_2$; Co. No.10; Ex. [B10]; mp. 142°C
	
. 0.23 $C_6H_{14}O$; Co. No.24; Ex. [B10]; mp. 110°C	
	
Co. No.31; Ex. [B5]; mp. 190°C	Co. No.25; Ex. [B11]; mp. 217°C
	
.0.82 $C_2HF_3O_2$.1.11 H_2O; Co. No.26; Ex. [B12]; mp. 115°C	.0.82 $C_2HF_3O_2$.0.82 H_2O; Co. No.32; Ex. [B12]; mp. 145°C
	
$C_2HF_3O_2$; Co. No.27; Ex. [B13]; mp. 158°C	Co. No.28; Ex. [B14]; mp. 217°C
	
Co. No.29; Ex. [B15]; mp. >260°C	Co. No.33; Ex. [B15]; mp. 230°C

	
Co. No.34; Ex. [B15]; mp. 202°C	Co. No.35; Ex. [B15]; mp. 211°C
	
Co. No.30; Ex. [B16]	Co. No.36; Ex. [B16]
	
Co. No.37; Ex. [B16]	Co. No.38; Ex. [B16]
	
Co. No.39; Ex. [B16]	Co. No.40; Ex. [B16]
	
Co. No.41; Ex. [B16]	Co. No.42; Ex. [B16]
	
Co. No.43; Ex. [B16]	Co. No.44; Ex. [B16]
	
Co. No.45; Ex. [B16]	

C. Pharmacological example:

The *in vitro* assay for inhibition of histone deacetylase (see example C.1) measures the inhibition of HDAC enzymatic activity obtained with the compounds of formula (I).

Cellular activity of the compounds of formula (I) was determined on A2780 tumour cells using a colorimetric assay for cell toxicity or survival (Mosmann Tim, Journal of Immunological Methods 65: 55-63, 1983)(see example C.2).

Kinetic solubility in aqueous media measures the ability of a compound to stay in aqueous solution upon dilution (see example C.3).
DMSO-stock solutions are diluted with a single aqueous buffer solvent in 3 consecutive steps. For every dilution turbidity is measured with a nephelometer.

A drug's permeability expresses its ability to move from one medium into or through another. Specifically its ability to move through the intestinal membrane into the blood stream and/or from the blood stream into the target. Permeability (see example C.4) can be measured through the formation of a filter-immobilized artificial membrane phospholipid bilayer. In the filter-immobilized artificial membrane assay, a "sandwich" is formed with a 96-well microtitre plate and a 96-well filter plate, such that each composite well is divided into two chambers with a donor solution at the bottom and an acceptor solution at the top, separated by a 125 µm micro-filter disc (0.45 µm pores), coated with 2%(wt/v) dodecane solution of dioleoylphosphatidyl-choline, under conditions that multi-lamellar bilayers form inside the filter channels when the system contacts an aqueous buffer solution. The permeability of compounds through this artificial membrane is measured in cm/s. The purpose is to look for the permeation of the drugs through a parallel artificial membrane at 2 different pH's: 4.0 and 7.4. Compound detection is done with UV-spectrometry at optimal wavelength between 250 and 500 nm.

Metabolism of drugs means that a lipid-soluble xenobiotic or endobiotic compound is enzymatically transformed into (a) polar, water-soluble, and excretable metabolite(s). The major organ for drug metabolism is the liver. The metabolic products are often less active than the parent drug or inactive. However, some metabolites may have enhanced activity or toxic effects. Thus drug metabolism may include both "detoxication" and "toxication" processes. One of the major enzyme systems that determine the organism's capability of dealing with drugs and chemicals is represented by the cytochrome P450 monooxygenases, which are NADPH dependent enzymes. Metabolic

stability of compounds can be determined *in vitro* with the use of subcellular human tissue (see example C.5). Here metabolic stability of the compounds is expressed as % of drug metabolised after 15 minutes incubation of these compounds with microsomes. Quantitation of the compounds was determined by LC-MS analysis.

The tumour suppressor p53 transcriptionally activates a number of genes including the WAF1/CIP1 gene in response to DNA damage. The 21 kDa product of the WAF1 gene is found in a complex involving cyclins, cyclin dependent kinases (CDKs), and proliferating cell nuclear antigen (PCNA) in normal cells but not transformed cells and appears to be a universal inhibitor of CDK activity. One consequence of p21WAF1 binding to and inhibiting CDKs is to prevent CDK-dependent phosphorylation and subsequent inactivation of the Rb protein, which is essential for cell cycle progression. Induction of p21WAF1 in response to cellular contact with a HDAC inhibitor is therefore a potent and specific indicator of inhibition of cell cycle progression at both the G1 and G2 checkpoints.
The capacity of the compounds to induce p21WAF1 was measured with the p21WAF1 enzyme linked immunosorbent assay (WAF1 ELISA of Oncogene). The p21WAF1 assay is a "sandwich" enzyme immunoassay employing both mouse monoclonal and rabbit polyclonal antibodies. A rabbit polyclonal antibody, specific for the human WAF1 protein, has been immobilized onto the surface of the plastic wells provided in the kit. Any p21WAF present in the sample to be assayed will bind to the capture antibody. The biotinylated detector monoclonal antibody also recognizes human p21WAF1 protein, and will bind to any p21WAF1, which has been retained by the capture antibody. The detector antibody, in turn, is bond by horseradish peroxidase-conjugated streptavidin. The horseradish peroxidase catalyses the conversion of the chromogenic substrate tetra-methylbenzidine from a colorless solution to a blue solution (or yellow after the addition of stopping reagent), the intensity of which is proportional to the amount of p21WAF1 protein bond to the plate. The colored reaction product is quantified using a spectrophotometer. Quantitation is achieved by the construction of a standard curve using known concentrations of p21WAF1 (provided lyophilised)(see example C.6).

Specific HDAC inhibitors should not inhibit other enzymes like the abundant CYP P450 proteins. The CYP P450 (E.coli expressed) proteins 3A4, 2D6 en 2C9 convert their specific substrates into a fluorescent molecule. The CYP3A4 protein converts 7-benzyloxy-trifluoromethyl coumarin (BFC) into 7-hydroxy-trifluoromethyl coumarin. The CYP2D6 protein converts 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC) into 3-[2-(N,N-diethylamino)ethyl]-7-hydroxy-4-

methylcoumarin hydrochloride and the CYP2C9 protein converts 7-Methoxy-4-trifluoromethyl coumarin (MFC) into 7-hydroxy-trifluoromethyl coumarin. Compounds inhibiting the enzymatic reaction will result in a decrease of fluoresent signal (see example C.7).

Example C.1: *In Vitro* Assay for Inhibition of histone deacetylase:

HeLa nuclear extracts (supplier: Biomol) were incubated at 60 µg/ml with $2x10^{-8}$ M of radiolabeled peptide substrate. As a substrate for measuring HDAC activity a synthetic peptide, i.e. the amino acids 14-21 of histone H4, was used. The substrate is biotinylated at the NH_2-terminal part with a 6-aminohexanoic acid spacer, and is protected at the COOH-terminal part by an amide group and specifically [^{3}H]acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-([^{3}H]-acetyl-Lys-Arg-His-Arg-Lys-Val-NH_2), was added in a buffer containing 25 mM Hepes, 1 M sucrose, 0.1 mg/ml BSA and 0.01% Triton X-100 at pH 7.4. After 30 min the deacetylation reaction was terminated by the addition of HCl and acetic acid. (final concentration 0.035 mM and 3.8 mM respectively). After stopping the reaction, the free ^{3}H-acetate was extracted with ethylacetate. After mixing and centrifugation, the radioactivity in an aliquot of the upper (organic) phase was counted in a β-counter.
For each experiment, controls (containing HeLa nuclear extract and DMSO without compound), a blank incubation (containing DMSO but no HeLa nuclear extract or compound) and samples (containing compound dissolved in DMSO and HeLa nuclear extract) were run in parallel. In first instance, compounds were tested at a concentration of 10^{-5}M. When the compounds showed activity at 10^{-5}M, a concentration-response curve was made wherein the compounds were tested at concentrations between 10^{-5}M and 10^{-12}M. In each test the blank value was substracted from both the control and the sample values. The control sample represented 100% of substrate deactylation. For each sample the radioactivity was expressed as a percentage of the mean value of the controls. When appropriate IC_{50}-values (concentration of the drug, needed to reduce the amount of metabolites to 50% of the control) were computed using probit analysis for graded data. Herein the effects of test compounds are expressed as pIC_{50} (the negative log value of the IC_{50}-value). All tested compounds showed enzymatic activity at a test concentration of 10^{-5}M and 42 compounds had a $pIC_{50} \geq 5$ (see table F-2).

Example C.2: Determination of antiproliferative activity on A2780 cells

All compounds tested were dissolved in DMSO and further dilutions were made in culture medium. Final DMSO concentrations never exceeded 0.1 % (v/v) in cell

proliferation assays. Controls contained A2780 cells and DMSO without compound and blanks contained DMSO but no cells. MTT was dissolved at 5 mg/ml in PBS. A glycine buffer comprised of 0.1 M glycine and 0.1 M NaCl buffered to pH 10.5 with NaOH (1 N) was prepared (all reagents were from Merck).

The human A2780 ovarian carcinoma cells (a kind gift from Dr. T.C. Hamilton [Fox Chase Cancer Centre, Pennsylvania, USA]) were cultured in RPMI 1640 medium supplemented with 2 mM L-glutamine, 50 μg/ml gentamicin and 10 % fetal calf serum. Cells were routinely kept as monolayer cultures at 37°C in a humidified 5 % CO_2 atmosphere. Cells were passaged once a week using a trypsin/EDTA solution at a split ratio of 1:40. All media and supplements were obtained from Life Technologies. Cells were free of mycoplasma contamination as determined using the Gen-Probe Mycoplasma Tissue Culture kit (supplier: BioMérieux).

Cells were seeded in NUNC™ 96-well culture plates (Supplier: Life Technologies) and allowed to adhere to the plastic overnight. Densities used for plating were 1500 cells per well in a total volume of 200 μl medium. After cell adhesion to the plates, medium was changed and drugs and/or solvents were added to a final volume of 200 μl. Following four days of incubation, medium was replaced by 200 μl fresh medium and cell density and viability was assessed using an MTT-based assay. To each well, 25 μl MTT solution was added and the cells were further incubated for 2 hours at 37°C. The medium was then carefully aspirated and the blue MTT-formazan product was solubilized by addition of 25 μl glycine buffer followed by 100 μl of DMSO. The microtest plates were shaken for 10 min on a microplate shaker and the absorbance at 540 nm was measured using an Emax 96-well spectrophotometer (Supplier: Sopachem). Within an experiment, the results for each experimental condition are the mean of 3 replicate wells. For initial screening purposes, compounds were tested at a single fixed concentration of 10^{-6} M. For active compounds, the experiments were repeated to establish full concentration-response curves. For each experiment, controls (containing no drug) and a blank incubation (containing no cells or drugs) were run in parallel. The blank value was subtracted from all control and sample values. For each sample, the mean value for cell growth (in absorbance units) was expressed as a percentage of the mean value for cell growth of the control. When appropriate, IC_{50}-values (concentration of the drug, needed to reduce cell growth to 50% of the control) were computed using probit analysis for graded data (Finney, D.J., Probit Analyses, 2nd Ed. Chapter 10, Graded Responses, Cambridge University Press, Cambridge 1962). Herein the effects of test compounds are expressed as pIC_{50} (the negative log value of the IC_{50}-value). Most of the tested compounds showed cellular activity at a test concentration of 10^{-6} M and 41 compounds had a $pIC_{50} \geq 5$ (see table F-2)

Example C.3: Kinetic solubility in aqueous media

In the first dilution step, 10 µl of a concentrated stock-solution of the active compound, solubilized in DMSO (5mM), was added to 100 µl phosphate citrate buffer pH 7.4 and mixed. In the second dilution step, an aliquot (20 µl) of the first dilution step was further dispensed in 100 µl phosphate citrate buffer pH 7.4 and mixed. Finally, in the third dilution step, a sample (20 µl) of the second dilution step was further diluted in 100 µl phosphate citrate buffer pH 7.4 and mixed. All dilutions were performed in 96-well plates. Immediately after the last dilution step the turbidity of the three consecutive dilution steps were measured with a nephelometer. Dilution was done in triplicate for each compound to exclude occasional errors. Based on the turbidity measurements a ranking is performed into 3 classes. Compounds with high solubility obtained a score of 3 and for this compounds the first dilution is clear. Compounds with medium solubility obtained a score of 2. For these compounds the first dilution is unclear and the second dilution is clear. Compounds with low solubility obtained a score of 1 and for these compounds both the first and the second dilution are unclear. The solubility of 9 compounds was measured. From these compounds 4 showed a score of 3, one obtained a score of 2 and 4 demonstrated a score of 1 (see table F-2).

Example C.4: Parallel artificial membrane permeability analysis

The stock samples (aliquots of 10 µl of a stock solution of 5 mM in 100 % DMSO) were diluted in a deep-well or Pre-mix plate containing 2 ml of an aqueous buffer system pH 4 or pH 7.4 (PSR4 System Solution Concentrate (pION)).
Before samples were added to the reference plate, 150 µl of buffer was added to wells and a blank UV-measurement was performed. Thereafter the buffer was discarded and the plate was used as reference plate. All measurements were done in UV-resistant plates (supplier: Costar or Greiner).
After the blank measurement of the reference plate, 150 µl of the diluted samples was added to the reference plate and 200 µl of the diluted samples was added to donorplate 1. An acceptor filter plate 1 (supplier: Millipore, type:MAIP N45) was coated with 4 µl of the artificial membrane-forming solution (1,2-Dioleoyl-sn-Glycer-3-Phosphocholine in Dodecane containing 0.1% 2,6-Di-tert-butyl-4-methylphenol and placed on top of donor plate 1 to form a "sandwich". Buffer (200 µl) was dispensed into the acceptor wells on the top. The sandwich was covered with a lid and stored for 18h at room temperature in the dark.
A blank measurement of acceptor plate 2 was performed through the addition of 150 µl of buffer to the wells, followed by an UV-measurement. After the blank measurement

of acceptor plate 2 the buffer was discarded and 150 µl of acceptor solution was transferred from the acceptor filter plate 1 to the acceptor plate 2. Then the acceptor filter plate 1 was removed form the sandwich. After the blank measurement of donor plate 2 (see above), 150 µl of the donor solution was transferred from donor plate 1 to donor plate 2. The UV spectra of the donor plate 2, acceptor plate 2 and reference plate wells were scanned (with a SpectraMAX 190). All the spectra were processed to calculate permeability with the PSR4p Command Software. All compounds were measured in triplo. Carbamazepine, griseofulvin, acycloguanisine, atenolol, furosemide, and chlorothiazide were used as standards in each experiment. Compounds were ranked in 3 categories as having a low permeability (mean effect $< 0.5 \times 10^{-6}$ cm/s; score 1), a medium permeability (1×10^{-6} cm/s > mean effect $\geq 0.5 \times 10^{-6}$ cm/s; score 2) or a high permeability ($\geq 0.5 \times 10^{-6}$ cm/s; score 3). Two of the 7 tested compounds showed at least a score of 2 at one of the pH's measured and 5 compounds showed only a score of 1 at one of the pH's measured.

Example C.5: Metabolic stability

Sub-cellular tissue preparations were made according to Gorrod *et al.* (Xenobiotica 5: 453-462, 1975) by centrifugal separation after mechanical homogenization of tissue. Liver tissue was rinsed in ice-cold 0.1 M Tris-HCl (pH 7.4) buffer to wash excess blood. Tissue was then blotted dry, weighed and chopped coarsely using surgical scissors. The tissue pieces were homogenized in 3 volumes of ice-cold 0.1 M phosphate buffer (pH 7.4) using either a Potter-S (Braun, Italy) equipped with a Teflon pestle or a Sorvall Omni-Mix homogeniser, for 7 x 10 sec. In both cases, the vessel was kept in/on ice during the homogenization process.

Tissue homogenates were centrifuged at 9000 x g for 20 minutes at 4 °C using a Sorvall centrifuge or Beckman Ultracentrifuge. The resulting supernatant was stored at -80 °C and is designated 'S9'.

The S9 fraction can be further centrifuged at 100.000 x g for 60 minutes (4 °C) using a Beckman ultracentrifuge. The resulting supernatant was carefully aspirated, aliquoted and designated 'cytosol'. The pellet was re-suspended in 0.1 M phosphate buffer (pH 7.4) in a final volume of 1 ml per 0.5 g original tissue weight and designated 'microsomes'.

All sub-cellular fractions were aliquoted, immediately frozen in liquid nitrogen and stored at -80 °C until use.

For the samples to be tested, the incubation mixture contained PBS (0.1M), compound (5 µM), microsomes (1mg/ml) and a NADPH-generating system (0.8 mM glucose-6-phosphate, 0.8 mM magnesium chloride and 0.8 Units of glucose-6-phosphate

dehydrogenase). Control samples contained the same material but the microsomes were replaced by heat inactivated (10 min at 95 degrees Celsius) microsomes. Recovery of the compounds in the control samples was always 100%.

The mixtures were preincubated for 5 min at 37 degrees Celsius. The reaction was started at timepoint zero (t = 0) by addition of 0.8 mM NADP and the samples were incubated for 15 min (t = 15). The reaction was terminated by the addition of 2 volumes of DMSO. Then the samples were centrifuged for 10 min at 900 x g and the supernatants were stored at room temperature for no longer as 24 h before analysis. All incubations were performed in duplo. Analysis of the supernatants was performed with LC-MS analysis. Elution of the samples was performed on a Xterra MS C18 (50 x 4.6 mm, 5 µm, Waters, US). An Alliance 2790 (Supplier: Waters, US) HPLC system was used. Elution was with buffer A (25 mM ammoniumacetate (pH 5.2) in H_2O/acetonitrile (95/5)), solvent B being acetonitrile and solvent C methanol at a flow rate of 2.4 ml/min. The gradient employed was increasing the organic phase concentration from 0 % over 50 % B and 50 % C in 5 min up to 100 % B in 1 min in a linear fashion and organic phase concentration was kept stationary for an additional 1.5 min. Total injection volume of the samples was 25 µl.

A Quattro (supplier: Micromass, Manchester, UK) triple quadrupole mass spectrometer fitted with and ESI source was used as detector. The source and the desolvation temperature were set at 120 and 350 °C respectively and nitrogen was used as nebuliser and drying gas. Data were acquired in positive scan mode (single ion reaction). Cone voltage was set at 10 V and the dwell time was 1 sec.

Metabolic stability was expressed as % metabolism of the compound after 15 min of incubation in the presence of active microsomes (E(act)) (% metabolism = 100 % - $\left(\left(\frac{\text{Total Ion Current (TIC) of E(act) at t = 15}}{\text{TIC of E(act) at t = 0}}\right) \times 100\right)$. Compounds that had a percentage metabolism less than 20 % were defined as highly metabolic stable. Compound that had a metabolism between 20 and 70 % were defined as intermediately stable and compounds that showed a percentage metabolism higher than 70 were defined as low metabolic stable. Three reference compounds were always included whenever a metabolic stability screening was performed. Verapamil was included as a compound with low metabolic stability (% metabolism = 73 %). Cisapride was included as a compound with medium metabolic stability (% metabolism 45 %) and propanol was included as a compound with intermediate to high metabolic stability (25 % metabolism). These reference compounds were used to validate the metabolic stability assay.

Eleven compounds were tested. Eight compounds had a percentage metabolism less than 20 %, two compounds had a percentage metabolism between 20 and 70 % and one compound showed a percentage metabolism higher than 70%.

Example C.6: p21 induction capacity

The following protocol has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. The A2780 cells (20000 cells /180 µl) were seeded in 96 microwell plates in RPMI 1640 medium supplemented with 2 mM L-glutamine, 50 µg/ml gentamicin and 10 % fetal calf serum. 24 hours before the lysis of the cells, compounds were added at final concentrations of 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} M. All compounds tested were dissolved in DMSO and further dilutions were made in culture medium. 24 hours after the addition of the compound, the supernatants were removed from the cells. Cells were washed with 200 µl ice-cold PBS. The wells were aspirated and 30 µl of lysisbuffer (50 mM Tris.HCl (pH 7.6), 150 mM NaCl, 1 % Nonidet p40 and 10 % glycerol) was added. The plates were incubated overnight at –70 °C.

The appropriate number of microtiter wells were removed from the foil pouch and placed into an empty well holder. A working solution (1x) of the Wash Buffer (20x plate wash concentrate: 100 ml 20-fold concentrated solution of PBS and surfactant. Contains 2 % chloroacetamide) was prepared. The lyophilised p21WAF standard was reconstituted with distilled H_2O and further diluted with sample diluent (provided in the kit)

The samples were prepared by diluting them 1:4 in sample diluent. The samples (100 µl) and the p21WAF1 standards (100 µl) were pipetted into the appropriate wells and incubated at room temperature for 2 hours. The wells were washed 3 times with 1x wash buffer and then 100 µl of detector antibody reagent (a solution of biotinylated monoclonal p21WAF1 antibody) was pipetted into each well. The wells were incubated at room temperature for 1 hour and then washed three times with 1x wash buffer. The 400x conjugate (peroxidase streptavidine conjugate: 400-fold concentrated solution) was diluted and 100 µl of the 1x solution was added to the wells. The wells were incubated at room temperature for 30 min and then washed 3 times with 1x wash buffer and 1 time with distilled H_2O. Substrate solution (chromogenic substrate)(100 µl) was added to the wells and the wells were incubated for 30 minutes in the dark at room temperature. Stop solution was added to each well in the same order as the previously added substrate solution. The absorbance in each well was measured using a spectrophotometric plate reader at dual wavelengths of 450/595 nm.

For each experiment, controls (containing no drug) and a blank incubation (containing no cells or drugs) were run in parallel. The blank value was substracted from all control and sample values. For each sample, the value for p21WAF1 induction (in absorbance units) was expressed as the percentage of the value for p21WAF1 present in the control. Percentage induction higher than 130 % was defined as significant induction. Thirteen compounds were tested in this assay. Eleven compounds showed significant induction.

Example C.7: P450 inhibiting capacity

All compounds tested were dissolved in DMSO (5 mM) and a further dilution to 5 10^{-4} M was made in acetonitrile. Further dilutions were made in assay buffer (0.1M NaK phosphate buffer pH 7.4) and the final solvent concentration was never higher than 2 %.

The assay for the CYP3A4 protein comprises per well 15 pmol P450/mg protein (in 0.01M NaKphosphate buffer + 1.15% KCl), an NADPH generating system (3.3 mM Glucose-6-phosphate, 0.4 U/ml Glucose-6-phosphate dehydrogenase, 1.3 mM NADP and 3.3 mM $MgCl_2.6H_2O$ in assay buffer) and compound in a total assay volume of 100 µl. After a 5 min pre-incubation at 37 °C the enzymatic reaction was started with the addition of 150 µM of the fluoresent probe substrate BFC in assay buffer. After an incubation of 30 minutes at room temperature the reaction was terminated after addition of 2 volumes of acetonitrile. Fluorescent determinations were carried out at an excitation wavelength of 405 nm and an emission wavelength of 535 nm. Ketoconazole (IC_{50}-value = 3 X 10^{-8}M) was included as reference compound in this experiment.

The assay for the CYP2D6 protein comprises per well 6 pmol P450/mg protein (in 0.01M NaKphosphate buffer + 1.15% KCl), an NADPH generating system (0.41 mM Glucose-6-phosphate, 0.4 U/ml Glucose-6-phosphate dehydrogenase, 0.0082 mM NADP and 0.41 mM $MgCl_2.6H_2O$ in assay buffer) and compound in a total assay volume of 100 µl. After a 5 min pre-incubation at 37 °C the enzymatic reaction was started with the addition of 3 µM of the fluoresent probe substrate AMMC in assay buffer. After an incubation of 45 minutes at room temperature the reaction was terminated after addition of 2 volumes of acetonitrile. Fluorescent determinations were carried out at an excitation wavelength of 405 nm and an emission wavelength of 460 nm. Quinidine (IC_{50}-value < 5 X 10^{-8} M) was included as reference compound in this experiment.

The assay for the CYP2C9 protein comprises per well 15 pmol P450/mg protein (in 0.01M NaKphosphate buffer + 1.15% KCl), an NADPH generating system (3.3 mM Glucose-6-phosphate, 0.4 U/ml Glucose-6-phosphate dehydrogenase, 1.3 mM NADP

and 3.3 mM $MgCl_2.6H_2O$ in assay buffer) and compound in a total assay volume of 100 µl. After a 5 min pre-incubation at 37 °C the enzymatic reaction was started with the addition of 200 µM of the fluoresent probe substrate MFC in assay buffer. After an incubation of 30 minutes at room temperature the reaction was terminated after addition of 2 volumes of acetonitrile. Fluorescent determinations were carried out at an excitation wavelength of 405 nm and an emission wavelength of 535 nm. Sulfaphenazole (IC_{50}-value = 6.8 X 10^{-7} M) was included as reference compound in this experiment.

For initial screening purposes, compounds were tested at a single fixed concentration of 1 X 10^{-6} M. For active compounds, the experiments were repeated to establish full concentration-response curves. For each experiment, controls (containing no drug) and a blank incubation (containing no enzyme or drugs) were run in parallel. All compounds were assayed in quadruplicate. The blank value was subtracted from all control and sample values. For each sample, the mean value of P450 activity of the sample (in relative fluorescence units) was expressed as a percentage of the mean value of P450 activity of the control. Percentage inhibition was expressed as 100% minus the mean value of P450 activity of the sample. When appropriate, IC_{50}-values (concentration of the drug, needed to reduce P450 activity to 50% of the control) were calculated. One compound was analysed in this assay. No inhibition of the different P450 enzymes could be detected with this compound.

Table F-2: Table F-2 lists the results of the compounds that were tested according to example C.1, C.2, and C.3.

Co. No.	Enzyme activity pIC50	Cellular activity pIC50	Solubility Score
1	6.523	5.277	
2	6.104	7.567	3
3	<5	5.744	
4	7.574	5.866	1
5	8.123	6.433	1
6	<5	5.68	
7	7.533	5.017	3
8	7.355	5.517	3
9	7.579	<5	2
10	6.893	5.673	
11	5.829	5.784	
12	7.438	5.536	

Co. No.	Enzyme activity pIC50	Cellular activity pIC50	Solubility Score
13	5.428	6.156	
14	6.116	5.68	
15	7.413	5.907	1
16	6.293	<5	
17	6.95	<5	
18	5.321	7.303	
19	<5	5.367	
20	7.294	5.556	1
21	8.199	6.441	
22	7.212	5.536	3
23	6.662	5.472	
24	7.903	5.97	
31	7.857	5.225	
25	6.449	<5	
32	7.526	6.255	
26	7.85	6.263	
27	7.49	5.781	
30	7.614	5.669	
36	7.265	5.977	
37	7.341	5.661	
38	7.154	5.937	
39	7.126	6.053	
40	7.273	6.164	
41	7.403	6.327	
42	7.584	6.342	
43	7.469	6.132	
44	7.432	6.192	
45	7.371	6.29	
28	7.074	5.109	
29	7.04	5.429	
33	6.837	5.653	
34	7.337	5.62	
35	7.046	5.935	

D. Composition example: Film-coated tablets

Preparation of tablet core

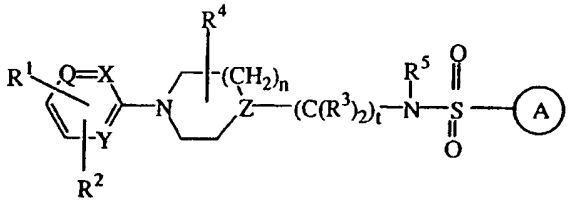
A mixture of 100 g of a compound of formula (I), 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulphate and 10 g polyvinyl-pyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there is added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of a compound of formula (I).

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinyl-pyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Claims

1. A compound of formula (I),



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

t is 0, 1, 2, 3 or 4 and when t is 0 then a direct bond is intended;

each Q is nitrogen or ;

each X is nitrogen or ;

each Y is nitrogen or ;

each Z is nitrogen or ;

R^1 is –C(O)NR^8R^9, -N(H)C(O)R^{10}, -C(O)-C_{1-6}alkanediylSR^{10}, -NR^{11}C(O)N(OH)R^{10}, -NR^{11}C(O)C_{1-6}alkanediylSR^{10}, -NR^{11}C(O)C=N(OH)R^{10} or another Zn-chelating-group

wherein R^8 and R^9 are each independently selected from hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl or aminoaryl;

R^{10} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, arylC_{1-6}alkyl, C_{1-6}alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

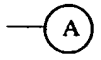
R^{11} is independently selected from hydrogen or C_{1-6}alkyl;

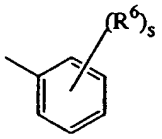
R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, di(C_{1-6}alkyl)amino, hydroxyamino or naphtalenylsulfonylpyrazinyl;

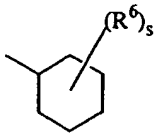
each R^3 independently represents a hydrogen atom and one hydrogen atom can be replaced by a substituent selected from aryl;

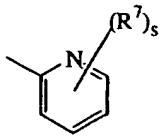
R^4 is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, hydroxycarbonyl, aminoC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyaminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

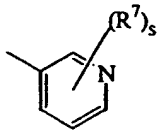
R^5 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl or aryl;

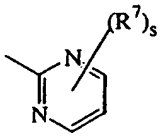

is a radical selected from

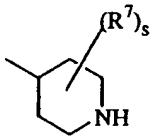

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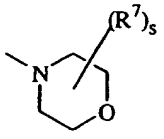

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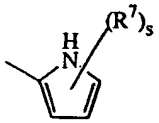

(a-3)

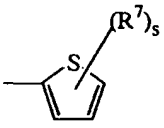

(a-4)

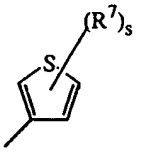

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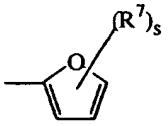

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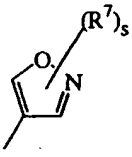

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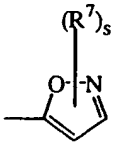

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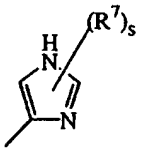

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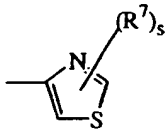

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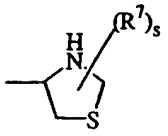

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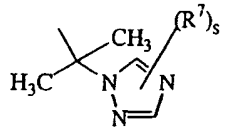

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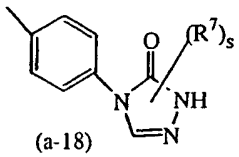

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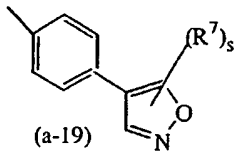

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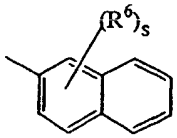
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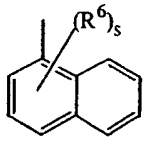
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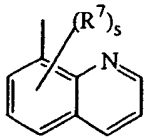
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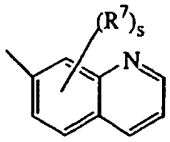
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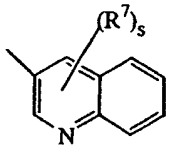
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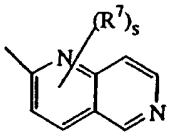
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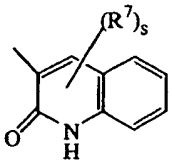
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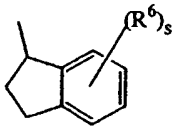
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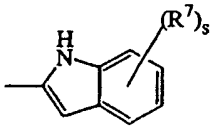
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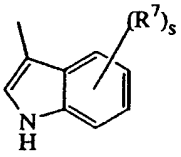
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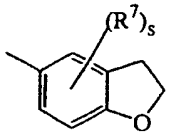
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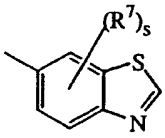
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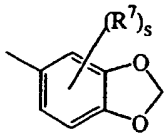
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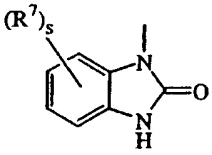
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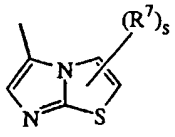
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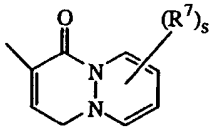
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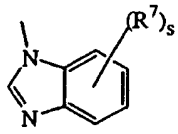
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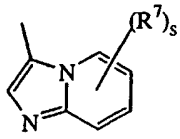
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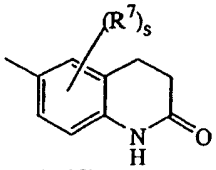
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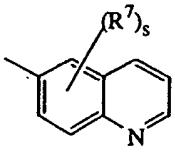
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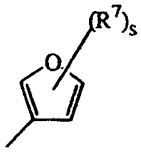
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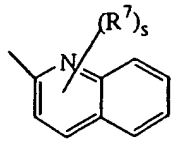
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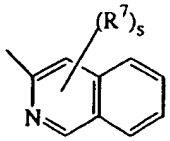


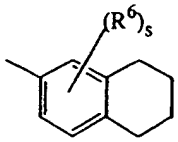
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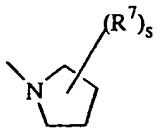


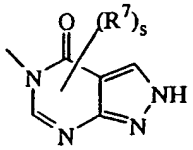
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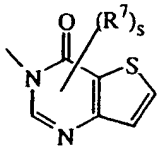

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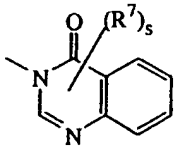

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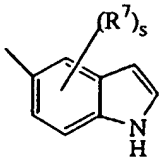

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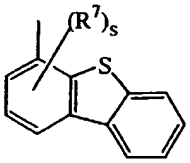

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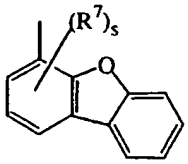

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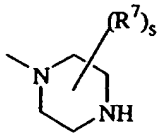

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(a-48)


(a-49)


(a-50)


(a-51)

wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R^6 and R^7 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyl substituted with aryl and C_{3-10}cycloalkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; cyanoC_{1-6}alkyl; hydroxyC_{1-6}alkyl; hydroxyC_{1-6}alkyloxy; hydroxyC_{1-6}alkylamino; aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminocarbonyl; di(hydroxyC_{1-6}alkyl)amino; (aryl)(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminoC_{1-6}alkylamino; di(C_{1-6}alkyl)aminoC_{1-6}alkylaminoC_{1-6}alkyl; arylsulfonyl; arylsulfonylamino; aryloxy; aryloxyC_{1-6}alkyl; arylC_{2-6}alkenediyl; di(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)amino(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)amino(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; aminosulfonylamino(C_{1-6}alkyl)amino; aminosulfonylamino(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylamino(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminosulfonylamino(C_{1-6}alkyl)aminoC_{1-6}alkyl; cyano; thiophenyl; thiophenyl substituted with di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylpiperazinylC_{1-6}alkyl, hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl, hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl,

di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl, C_{1-6}alkyloxypiperidinyl, C_{1-6}alkyloxypiperidinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxyC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, or di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; furanyl; furanyl substituted with hydroxyC_{1-6}alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}alkyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; piperidinylC_{1-6}alkyloxy; morpholinyl; C_{1-6}alkylmorpholinyl; morpholinylC_{1-6}alkyloxy; morpholinylC_{1-6}alkyl; morpholinylC_{1-6}alkylamino; morpholinylC_{1-6}alkylaminoC_{1-6}alkyl; piperazinyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinylC_{1-6}alkyloxy; piperazinylC_{1-6}alkyl; naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl; C_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkylpiperazinylC_{1-6}alkylamino; C_{1-6}alkylpiperazinylC_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC_{1-6}alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylpiperazinyl; di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl; hydroxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkyloxypiperidinyl; C_{1-6}alkyloxypiperidinylC_{1-6}alkyl; piperidinylaminoC_{1-6}alkylamino; piperidinylaminoC_{1-6}alkylaminoC_{1-6}alkyl; (C_{1-6}alkylpiperidinyl)(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkylamino; (C_{1-6}alkylpiperidinyl)(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkylaminoC_{1-6}alkyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)amino; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl; hydroxyC_{1-6}alkylaminoC_{1-6}alkyl; di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy, aryloxy or aryl; pyrimidinyl; tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC_{1-6}alkyl; quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC_{1-4}alkyloxy, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxyC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminocarbonyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)amino(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)amino(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)aminoC_{1-4}alkyl,

aminosulfonylamino(C_{1-4}alkyl)amino,
aminosulfonylamino(C_{1-4}alkyl)aminoC_{1-4}alkyl,
di(C_{1-4}alkyl)aminosulfonylamino(C_{1-4}alkyl)amino,
di(C_{1-4}alkyl)aminosulfonylamino(C_{1-4}alkyl)aminoC_{1-6}alkyl, cyano,
piperidinylC_{1-4}alkyloxy, pyrrolidinylC_{1-4}alkyloxy, aminosulfonylpiperazinyl,
aminosulfonylpiperazinylC_{1-4}alkyl, di(C_{1-4}alkyl)aminosulfonylpiperazinyl,
di(C_{1-4}alkyl)aminosulfonylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylpiperazinyl,
hydroxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkyloxypiperidinyl,
C_{1-4}alkyloxypiperidinylC_{1-4}alkyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinyl,
hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinylC_{1-4}alkyl,
(hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)amino, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)aminoC_{1-4}alkyl,
di(hydroxyC_{1-4}alkyl)amino, di(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkyl, furanyl, furanyl
substituted with –CH=CH-CH=CH-, pyrrolidinylC_{1-4}alkyl, pyrrolidinylC_{1-4}alkyloxy,
morpholinyl, morpholinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyl,
morpholinylC_{1-4}alkylamino, morpholinylC_{1-4}alkylaminoC_{1-4}alkyl, piperazinyl,
C_{1-4}alkylpiperazinyl, C_{1-4}alkylpiperazinylC_{1-4}alkyloxy, piperazinylC_{1-4}alkyl,
C_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkylpiperazinylC_{1-4}alkylamino,
C_{1-4}alkylpiperazinylC_{1-4}alkylaminoC_{1-6}alkyl, tetrahydropyrimidinylpiperazinyl,
tetrahydropyrimidinylpiperazinylC_{1-4}alkyl, piperidinylaminoC_{1-4}alkylamino,
piperidinylaminoC_{1-4}alkylaminoC_{1-4}alkyl,
(C_{1-4}alkylpiperidinyl)(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkylamino,
(C_{1-4}alkylpiperidinyl)(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkylaminoC_{1-4}alkyl,
pyridinylC_{1-4}alkyloxy, hydroxyC_{1-4}alkylamino, hydroxyC_{1-4}alkylaminoC_{1-4}alkyl,
di(C_{1-4}alkyl)aminoC_{1-4}alkylamino, aminothiadiazolyl,
aminosulfonylpiperazinylC_{1-4}alkyloxy, or thiophenylC_{1-4}alkylamino;
each R^6 and R^7 can be placed on the nitrogen in replacement of the hydrogen;

aryl in the above is phenyl, or phenyl substituted with one or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

2. A compound as claimed in claim 1 wherein n is 0, 1 or 2; t is 0, 1, 2 or 3; each Q is —C<; R^1 is –C(O)NH(OH) or –NR^{11}C(O)C=N(OH)R^{10} wherein R^{10} is arylC_{1-6}alkyl and R^{11} is hydrogen; R^2 is hydrogen, C_{1-6}alkyl or naphtalenylsulfonylpyrazinyl; each R^3 independently represents a hydrogen atom; R^4 is hydrogen, hydroxy, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxy; R^5 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; —(A) is a radical selected

from (a-1), (a-7) or (a-20); each s is independently 0 or 1; each R^6 is independently selected from hydrogen; thiophenyl; furanyl; benzofuranyl; phenyl; or phenyl substituted with one substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, C_{1-4}alkylsulfonyl or di(C_{1-4}alkyl)amino and each R^7 is independently selected from hydrogen.

3. A compound according to claim 1 wherein t is 0;

R^1 is $-C(O)NR^8R^9$, $-C(O)-C_{1-6}alkanediylSR^{10}$, $-NR^{11}C(O)N(OH)R^{10}$, $-NR^{11}C(O)C_{1-6}alkanediylSR^{10}$, $-NR^{11}C(O)C=N(OH)R^{10}$ or another Zn-chelating-group wherein R^8 and R^9 are each independently selected from hydrogen, hydroxy, hydroxyC_{1-6}alkyl or aminoC_{1-6}alkyl;

R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl or di(C_{1-6}alkyl)amino;

R^4 is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^5 is hydrogen;


is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) or (a-51);

each s is independently 0, 1, 2, 3 or 4;

R^6 is hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; thiophenyl; furanyl; furanyl substituted with hydroxyC_{1-6}alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}alkyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; C_{1-6}alkylmorpholinyl; piperazinyl; C_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinyl; C_{1-6}alkyloxypiperidinyl; pyrazoly; pyrazolyl substituted with one or two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy, aryloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl; and

R^7 is hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl;

hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; pyridinyl; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

4. A compound as claimed in claim 1 wherein

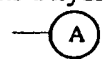
R^8 and R^9 are each independently selected from hydrogen, hydroxy, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl or aminoaryl;

R^5 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

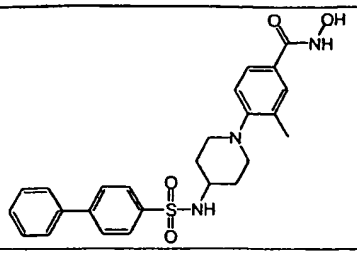
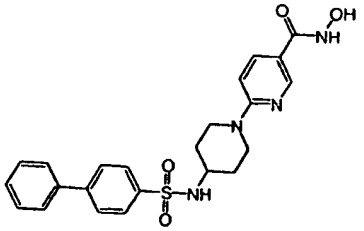
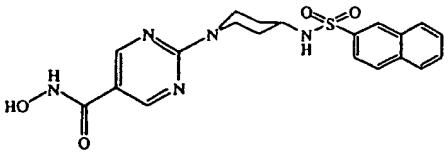
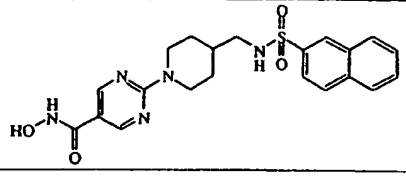
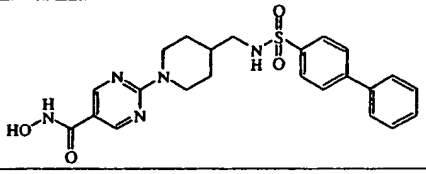
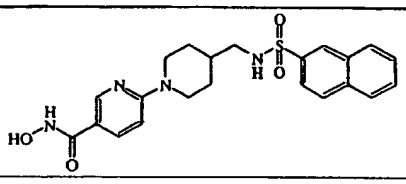
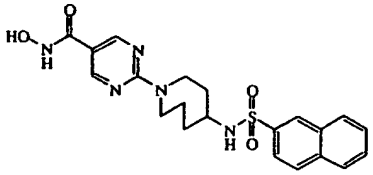
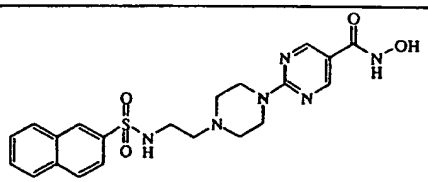
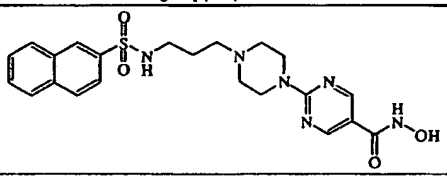
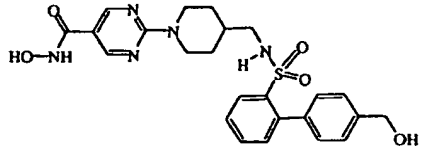
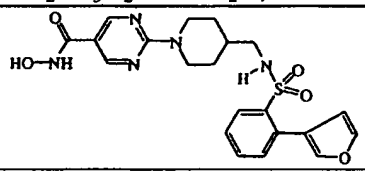
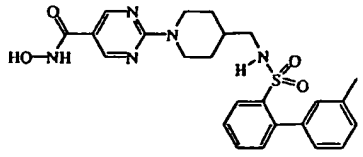
—(A) is a radical selected from (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-27), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42) (a-43) or (a-44);

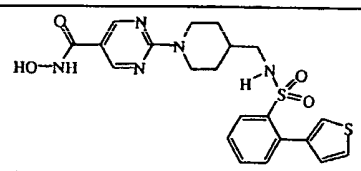
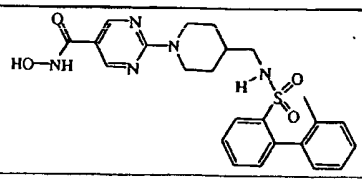
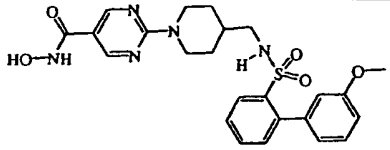
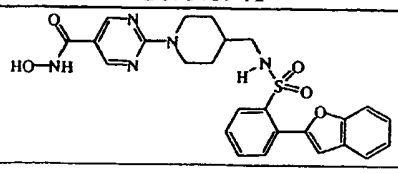
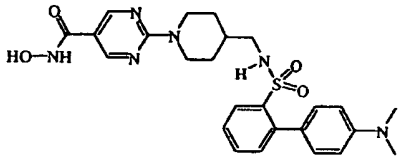
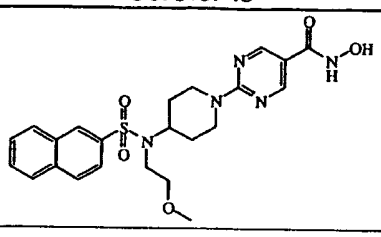
each R^6 and R^7 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkylsulfonyl; cyanoC_{1-6}alkyl; hydroxyC_{1-6}alkyl; hydroxyC_{1-6}alkyloxy; hydroxyC_{1-6}alkylamino; aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminocarbonyl; di(hydroxyC_{1-6}alkyl)amino; arylC_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminoC_{1-6}alkylamino; arylsulfonyl; arylsulfonylamino; aryloxy; arylC_{2-6}alkenediyl; di(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; cyano; thiophenyl; thiophenyl substituted with di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylpiperazinylC_{1-6}alkyl or di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; furanyl; imidazolyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; piperidinylC_{1-6}alkyloxy; morpholinyl; C_{1-6}alkylmorpholinyl; morpholinylC_{1-6}alkyloxy; morpholinylC_{1-6}alkyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinylC_{1-6}alkyloxy; C_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC_{1-6}alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylpiperazinyl; di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl; hydroxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkyloxypiperidinyl; C_{1-6}alkyloxypiperidinylC_{1-6}alkyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl;

(hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)amino; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC_{1-4}alkyloxy, C_{1-4}alkyloxyC_{1-4}alkyloxy, aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)aminoC_{1-4}alkyl, piperidinylC_{1-4}alkyloxy, pyrrolidinylC_{1-4}alkyloxy, aminosulfonylpiperazinyl, aminosulfonylpiperazinylC_{1-4}alkyl, di(C_{1-4}alkyl)aminosulfonylpiperazinyl, di(C_{1-4}alkyl)aminosulfonylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylpiperazinyl, hydroxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkyloxypiperidinyl, C_{1-4}alkyloxypiperidinylC_{1-4}alkyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)amino, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)aminoC_{1-4}alkyl, pyrrolidinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyl, C_{1-4}alkylpiperazinyl, C_{1-4}alkylpiperazinylC_{1-4}alkyloxy, C_{1-4}alkylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylamino, di(hydroxyC_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminoC_{1-4}alkylamino, aminothiadiazolyl, aminosulfonylpiperazinylC_{1-4}alkyloxy, or thiophenylC_{1-4}alkylamino.

5. A compound as claimed in claim 1 and 2 wherein n is 1 or 2; t is 0, 1, 2 or 3; each Q is ; R^1 is –C(O)NH(OH); R^2 is hydrogen or C_{1-6}alkyl; each R^3 independently represents a hydrogen atom; R^4 is hydrogen; R^5 is hydrogen or C_{1-6}alkyloxyC_{1-6}alkyl;  is a radical selected from (a-1) or (a-20); each s is independently 0 or 1; and each R^6 is independently selected from hydrogen; thiophenyl; furanyl; benzofuranyl; phenyl; or phenyl substituted with one substituents independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl or di(C_{1-4}alkyl)amino.

6. A compound according to claim 1, 2 and 5 selected from compounds No. 13, No. 15, No. 2, No. 5, No. 21, No. 4, No. 24, No. 32, No. 26, No. 36, No. 38, No. 39, No. 40, No. 41, No. 42, No. 43, No. 44 and No. 35.

	
Co. No. 13	Co. No. 15
	
Co. No. 2	Co. No. 5
	
.0.7 CH_3OH; Co. No. 21	Co. No. 4
	
.0.23 $C_6H_{14}O$; Co. No. 24	.0.82 $C_2HF_3O_2$.0.82 H_2O; Co. No. 32
	
.0.85 $C_2HF_3O_2$.1.11 H_2O; Co. No. 26	Co. No. 36
	
Co. No. 38	Co. No. 39

	
Co. No. 40	Co. No. 41
	
Co. No. 42	Co. No. 43
	
Co. No. 44	Co. No. 35

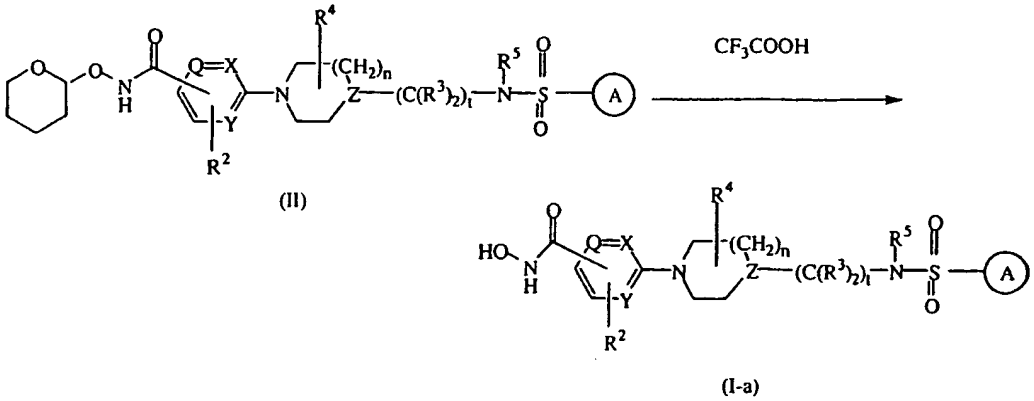
7. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 6.

8. A process of preparing a pharmaceutical composition as claimed in claim 7 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 6 are intimately mixed.

9. A compound as claimed in any of claims 1 to 6 for use as a medicine.

10. Use of a compound as claimed in any of claims 1 to 6 for the manufacture of a medicament for the treatment of proliferative diseases.

11. A process for preparing a compound as claimed in claim 1, characterized by reacting an intermediate of formula (II) with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I-a), wherein R^1 is –C(O)NH(OH)



12. A method of detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound as defined in claim (I) and a HDAC.

13. A combination of an anti-cancer agents and a HDAC inhibitor as claimed in any of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02517

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D401/04 C07D207/14 C07D403/04 A61K31/4545
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 38322 A (METHYLGENE INC) 31 May 2001 (2001-05-31) the whole document	1,10
A	WO 98 55449 A (QUEENSLAND INST MED RES ;FAIRLIE DAVID (AU); PARSONS PETER G (AU);) 10 December 1998 (1998-12-10) the whole document	1,10
A	PAN P-C ET AL: "Soluble Polymer-Supported Synthesis of Arylpiperazines" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9505-9508, XP004144238 ISSN: 0040-4039 compound 10	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2003	22/05/2003

Name and mailing address of the ISA	Authorized officer
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Information on patent family members

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